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THE ELECTRO-ENCEPHALOGRAM IN ADDISON'S DISEASE[1]

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Submitted for publication February 10, 1942

INTRODUCTION

It is well known that patients with Addison's disease exhibit a characteristic progression of metabolic changes during the onset of acute adrenal cortical insufficiency (1). It would appear that adrenal cortical insufficiency might modify the metabolism of nervous tissue as a consequence of (a) a decrease in circulation, (b) an alteration in electrolyte concentration, and (c) a disturbance in carbohydrate metabolism.

In 1936 Derbyshire (2) followed the changes in the electro-encephalogram of a patient with Addison's disease during recovery from an acute adrenal crisis. Although striking abnormalities were observed in the initial electro-encephalogram and in subsequent tracings taken during the period of recovery, it was considered that the state of collapse which characterized the clinical condition of this patient precluded the attachment of any specific significance to the changes in the electro-encephalogram. Recently, Engel and Morgolin (3) have studied the electro-encephalograms of six patients with Addison's disease and have reported on the relationship between changes in the sensitivity of the electro-encephalograms to hyperventilation and alterations in carbohydrate metabolism.

The present investigation was undertaken to determine whether abnormalities occurred regularly in the electro-encephalograms of patients with Addison's disease. Studies on 25 patients with classical signs and symptoms of Addison's disease form the basis of this report. Electro-encephalographic records were obtained during standard conditions, during voluntary hyperventilation, and, in some instances,

[1] This study was aided by a grant from the Committee on Research in Endocrinology, National Research Council.

[2] John D. Archbold Fellow in Medicine.

during exposure to hypoxia. In 24 of 25 patients, electro-encephalograms were made during the course of treatment with desoxycorticosterone acetate at a time when the patient's condition was considered to be relatively good, and when the blood pressure and values for chemical constituents of the blood approximated normal. Three patients were studied before desoxycorticosterone acetate therapy was instituted. The effect of aqueous adrenal cortical extract therapy (presumably containing all known adrenal cortical factors), of treatment with crystalline components of the vitamin B complex, of glucose administered intravenously (because of the intimate relationship of these substances to carbohydrate metabolism), and of a diet high in readily available carbohydrates were also investigated.

METHODS

A Grass ink-writing 6 channel instrument with a paper speed of 30 mm. per second was employed. In most instances the silver chloride electrodes were placed bilaterally in frontal, pre-central, parietal, and occipital regions, approximately 3.5 cm. from the mid-line. Monopolar and bipolar tracings were obtained, the former being referred to the left mastoid process.

Sensitivity to voluntary hyperventilation was estimated by measuring the time which elapsed before large, slow waves appeared. Large slow waves were considered to be those with a potential change of twice the amplitude of preceding waves and a rate of 4 per second, or less.

Sensitivity to low oxygen tension was studied by administering 12 per cent oxygen (in nitrogen) for a period of 10 minutes. A dry meter was used to measure the respiratory volume before, during and after the exposure.

OBSERVATIONS

I. The electro-encephalogram during rest

The outstanding feature in 18 of 25 patients was the regular occurrence of oscillations slower than the normal alpha rhythm (Table 1). This abnormality was characterized by a well defined rhythm which was present for varying periods. However, the rhythm was less regular with respect to frequency and amplitude than the normal alpha rhythm. Waves with a frequency of 5, 6 or 7 per second occurred

TABLE 1

NAME	SEX	AGE	BLOOD PRESSURE	"CARBOHYDRATE DEFECT"[1]	BLOOD CHEMISTRY				TREATMENT		CLINICAL STATE	FRONTAL PART OF CORTEX					OCCIPITAL PART OF CORTEX				PREPONDERANCE[5]
												Slow activity				Fast activity	Alpha and slow activity				
					Na	K	Cl	CO_2	Kind	Duration		Frequency	"Rhythm" time[4]	Regularity	Amplitude		Frequency	"Rhythm" time[4]	Regularity	Amplitude	
			mm. Hg		*m. eq. per l. serum*										*microvolts*					*microvolts*	
A. T.	M	49	156/108	moderate	136	3.7	105	27.2	pellets[2]	13½ months	good	6–8	dominant	fair	50	normal	7	episodes	fair	30	Frontal
H. S.	M	48	110/70	slight	138	5.4	103	25.9	NaCl		good	7	dominant	fair	40–50	reduced	9	dominant	fair	25	Frontal
A. P.	M	45	110/74	moderate	141	4.3	105	30.0	Percorten[3]	9 days	good			none	15	reduced	11	episodes	poor	15	none
F. D.	M	43	118/76	moderate	136	4.2	107	25.4	pellets	27 months	fair	7	half-time	good	50–80	reduced	7	dominant	good	40	Frontal
E. V.	M	42	106/72	moderate	138	5.3	103	23.7	pellets	27½ months	fair	6–7	dominant	good	40	reduced	6–9	dominant	fair	25	Frontal
P. W.	M	36	124/90	marked	137	4.6	105	25.4	pellets	27 months	fair	5–7	dominant	good	40–80	reduced	8	dominant	fair	20–30	Frontal
F. M.	M	34	130/80	moderate	142	4.4	109	30.8	pellets	31 months	good	7½	episodes	poor	25–30	normal	7–9	dominant	good	30–60	Occipital
C. F.	M	33	95/70	marked	136	4.3	97	26.8	NaCl		poor	5–8	episodes	poor	50–100	increased	7–8	dominant	good	50	Frontal
W. C.	M	27	128/94	slight	138	3.8	101	27.2	pellets	12½ months	good	5–6	episodes	fair	40	reduced	5–9	dominant	poor	25–40	Frontal
J. H.	M	24	112/70	moderate	138	5.5	103	29.5	pellets	20½ months	good	6–7	half-time	good	30–80	normal	8–10	dominant	poor	30–40	Frontal
F. H.	M	23	140/100	moderate	143	4.2	105	29.9	pellets	14½ months	fair	6–8	dominant	good	50–130	reduced	7–9	dominant	fair	40–65	Frontal
S. B.	M	22	120/80	marked		5.6	106	24.6	pellets	12 days	good	6	dominant	good	40–100	normal	8	dominant	fair	40–50	Frontal
W. B.	M	22	130/90	marked	135	4.8	98	28.1	pellets	19 months	good	7	dominant	good	40–75	reduced	8	dominant	fair	60–75	Occipital
S. W.	F	56	136/100	slight	138	3.6	104	26.3	pellets	18½ months	good	7½	half-time	poor	30	increased	8	dominant	fair	60	Occipital
A. G.	F	51	120/76	slight	135	5.3	103	24.1	pellets	10½ months	fair	6–8	dominant	fair	25–30	increased	6–7	dominant	fair	15	Frontal
E. L.	F	51	128/88	marked	138	3.2	100	28.1	pellets	6 months	poor	8	half-time	fair	25–30	increased	9	dominant	good	25–30	none
E. F.	F	50	148/100	slight	139	6.4	105	24.6	pellets	4½ months	good			none	25	increased			none	25	none
L. V.	F	43	122/76	slight	134	6.6	98	28.1	Percorten	9 days	fair			none	30	increased			none	20	Frontal
A. H.	F	40	128/82	slight	135	6.4	105	27.6	pellets	17 months	fair	6–8	dominant	good	60–125	reduced	7–8	dominant	fair	50–60	Frontal
M. S.	F	38	120/80	moderate	140	3.7	108	29.9	pellets	9 days	fair	6–7	dominant	good	60	reduced	6	dominant	fair	50–60	none
M. N.	F	37	96/80	moderate	132	5.0	106	25.0			fair	6–7		none	25	increased	9		poor	60	Occipital
I. H.	F	36	128/80	moderate	136	5.6	106	27.2	pellets	12 months	good	6	episodes	fair	−100	reduced			none	25–40	Frontal
H. U.	F	34	110/82	moderate	138	4.9	108	26.8	pellets	3 days	fair	5–6	(random)	poor	25–30	increased	6–9	dominant	fair	40–60	Occipital
A. H.	F	21	120/88	slight		5.0	107	24.0	pellets	14½ months	good	6	(random)	poor	40	normal	7–8		poor	30–40	none
K. D.	F	19	120/80	moderate	142	4.9	106	26.3	pellets	9 days	good			none	10	increased	7–9	episodes	poor	30	none

[1] Carbohydrate defect: fasting hypoglycemia or abnormal glucose curve following intravenously administered glucose.
[2] Pellets: crystalline synthetic desoxycorticosterone acetate prepared by Ciba Pharmaceutical Products, Inc., Summit, N. J.
[3] Percorten: synthetic desoxycorticosterone acetate in oil prepared by Ciba Pharmaceutical Products, Inc., Summit, N. J.
[4] Rhythm time: analogous to "alpha time", indicating to what extent the abnormal slow rhythm was present.
[5] Preponderance: the location in which the abnormal slow rhythm (when present) appeared to be most pronounced.

singly or in sequences, and a sequence of one of these frequencies was often interrupted by slow waves of a slightly different frequency. Equally variable was the amplitude. Random large waves with amplitudes of 75 to 150 microvolts occurred singly and in sequence. The increase in amplitude did not develop gradually, as is the case with the normal alpha tide, but more abruptly. The usual well known correlation between increment and decrement of amplitudes and periods was observed.

Regional or generalized runs of large 3–5 per second waves were encountered in a few patients as well as random, blunt, spike-and-wave forms.

In 13 of the 18 cases in which an abnormal rhythm was found, it was noted that the abnormality was more pronounced over the anterior portion of the brain, i.e. the waves were of larger amplitude and were more regular. However, in one patient (W. B.) the rhythm was more pronounced in the occipital region, and in two patients (F. M., H. U.) the slow rhythm abnormality was present only in the occipital region. In one patient (M. S.) the slow rhythm was equal in its distribution over the brain.

The abnormal rhythm in the resting pattern was affected relatively little by opening of the eyes. One would not expect visual stimulation to produce a marked change in the patients in whom the abnormal slow rhythm was not well developed. However, even in the patients with a very well developed abnormal slow rhythm only a slight depression of the rhythm (in the frontal region) was observed for a few seconds after the eyes were opened, following which the rhythm continued very much as before. In no instance did we note speeding up of the rhythm immediately following closing of the eyes.

Low voltage, fast frequency waves (beta waves) were either absent or greatly decreased in number in 13 of the 25 patients. It appeared that the reduction in number or the absence of beta waves was correlated to some extent with the presence of the abnormal slow rhythm; six of the 8 patients in whom the slow rhythm was most pronounced, showed an absence of beta rhythm, whereas the beta waves were present in 6 of the 7 patients in whom the abnormal slow rhythm was not observed.

In some patients the bipolar recording gave an unusually flat picture,

pointing to a high degree of synchronization between different regions. The synchronization occurred in the high frequency activity—so far it was present with monopolar technique—and also reduced the amplitudes and rounded the forms of the slower activity.

II. The effect of voluntary hyperventilation

The changes which were observed in patients with Addison's disease during voluntary hyperventilation were similar to those which are well known in normal persons, except that the changes occurred much earlier. After an initial phase in which a slight increase in period and amplitude was noted, a single, large, slow wave of irregular form occurred. Somewhat later a burst of 3 or 4 such waves was seen, and then sequences of irregular, large, slow waves dominated the picture. Finally, the well known record of regular, smooth, large three-per-second waves developed.

A definite relation seemed to exist between the slow wave abnormality in the resting pattern and the appearance of large, slow waves during hyperventilation. Of 7 patients with no electro-encephalographic abnormalities during rest, 6 did not develop large, slow waves during hyperventilation; whereas in 14 patients with definite positive findings during rest, all but one displayed high sensitivity to hyperventilation.

Of the 22 patients who were tested for the effect of hyperventilation, 4 responded with large slow waves in the first minute, 5 in the second minute and 6 in the third minute. Two of these patients had normal patterns of the electro-encephalogram during rest.

III. The effect of exposure to low oxygen partial pressure

The changes which occurred in the electro-encephalogram during exposure to 12 per cent oxygen in nitrogen (approximately 91 mm. Hg. oxygen partial pressure) for a period of 10 minutes were studied in 5 patients with Addison's disease. Large slow waves occurred in 3 of these patients (W. C., F. H., and C. F.) in 3, 3 and 6 minutes respectively. The fact that the large slow waves occurred in one of the patients (W. C.) in spite of a slight decrease in respiratory volume suggests that anoxia rather than acapnia was responsible for this change in the electro-encephalogram.

It was noted that 3 patients who reacted to hypoxia with large slow waves also displayed a marked sensitivity (in electro-encephalogram) to hyperventilation, whereas in one patient (A. P.) neither hypoxia nor hyperventilation induced large slow waves. These observations suggested that there was a similarity in the sensitivity of the electro-encephalogram to changes in the concentration of oxygen and changes in the concentration of carbon dioxide. However, one patient (W. B.) who failed to develop large slow waves during exposure to low oxygen partial pressure did develop large slow waves during hyperventilation.

IV. Effect of treatment

A. Hormonal substances: Typical abnormalities in the resting pattern of the electro-encephalogram were observed in 17 of 24 patients with Addison's disease who had been treated with a quantity of desoxycorticosterone acetate (pellets of crystalline hormone implanted subcutaneously or intramuscular injections of hormone in oil) which was sufficient to maintain plasma volume, blood pressure, body weight and electrolyte balance.

In 3 patients it was possible to study the electro-encephalogram prior to synthetic hormone therapy. One of these patients (H. S.) was observed to have a pronounced abnormality in the electro-encephalogram during rest. One (C. F.) had slight abnormalities and one (M. N.) showed a normal pattern prior to hormone therapy. The last patient showed an abnormal pattern after 1 year of synthetic hormone therapy.

Further observations on the relation between hormone therapy and abnormalities of the electro-encephalogram during rest have been grouped as follows:

Four patients showed a normal electro-encephalogram during rest, following 4 to 27 months of continued synthetic hormone therapy.

Four patients with abnormalities in the electro-encephalogram during rest failed to show any progression in the abnormality during one year of continued hormone therapy.

However, 3 patients showed a pronounced increase of abnormal features when the electro-encephalogram was repeated after one year of synthetic hormone therapy. One of these was the patient (M. N.) who, before the treatment started, had shown a normal pattern.

In none of the patients was the abnormality of the resting pattern abolished or improved by synthetic hormone treatment. Furthermore, the addition of 4–8 cc daily of adrenal cortical extract failed to correct the abnormal resting pattern. Treatment with large quantities of adrenal cortical extract alone was not tried.

The electro-encephalographic sensitivity to hyperventilation, on the other hand, was improved in some patients during periods of treatment with adrenal hormone. Two patients (C. F., A. H.) showed a definite decrease in sensitivity to hyperventilation during a short period of treatment with synthetic hormone and adrenal extract.

Two patients (J. H., A. T.) showed decreased sensitivity to hyperventilation after one year of continued treatment with synthetic hormone despite no improvement of the electro-encephalogram during rest. Two patients (M. N., M. S.) showed decreased sensitivity to hyperventilation during one year of treatment with synthetic hormone despite a definite increase in the abnormalities of the resting pattern.

B. Fractions of the vitamin B complex: Combined treatment with 15–30 mg of thiamin hydrochloride, 7.5–15 mg of riboflavin, 75–150 mg of nicotinic acid and 120–240 mg of vitamin B_6 and calcium pantothenate,[3] daily for a period of 2–4 weeks failed to correct the abnormality in the resting pattern of the electro-encephalogram of four patients with Addison's disease.

C. Glucose: The intravenous injection of 10 gm of glucose did not produce any certain modification of the abnormality in the resting pattern of patients with Addison's disease. The sensitivity to hyperventilation, however, was significantly reduced in 2 patients (A. H., I. H.): Furthermore, the clinical condition of the patients during hyperventilation and the efficiency of overbreathing were both greatly improved. Two patients (C. F., F. H.) were able to increase respiratory volume 30 and 40 per cent respectively when hyperventilation was conducted immediately after intravenous glucose administration.

[3] TRN 6 P tablets containing 5 mg. of thiamin hydrochloride, 2.5 mg. of riboflavin, 25 mg. of nicotinic acid and 40 mg. of vitamin B_6, calcium pantothenate equivalent to 20 mg. of pantothenic acid, were provided for this study through the courtesy of Merck and Co., Inc., Rahway, N. J. In any capsule which contains riboflavin as well as thiamin, rapid decomposition of the thiamin may occur (L. E. Holt, Personal Communication).

Maintaining patients on a high carbohydrate diet (6–8 gm carbohydrate per Kg body weight per day) with frequent intermediate feedings of carbohydrate did not appear to modify the abnormality in the resting pattern of the electro-encephalogram or in the response to hyperventilation. The ingestion of food immediately prior to the recording of the electro-encephalogram did not prevent the appearance of the abnormal slow activity of the resting pattern.

V. Control studies

Electro-encephalograms of 9 patients with hypotension and fatigue in whom there was no additional clinical or laboratory evidence of Addison's disease failed to reveal the abnormality in the resting pattern which had been observed in 18 of 25 patients with Addison's disease. However, 2 of these hypotensive, asthenic patients did have an increased sensitivity to hyperventilation

It is well known that low oxygen partial pressure has a tendeny to increase amplitudes and wavelengths (6). For purposes of control, the effect of exposure to 12 per cent oxygen was studied in another 9 subjects without Addison's disease or hypotension. Six of them, (4 healthy subjects and 2 patients with neuroses) did not show any significant changes, but 3 other subjects, (a 15-year old healthy boy, a patient with epilepsy and a patient with schizophrenia in whom electro-encephalographic changes were present following electro-shock therapy) showed large slow waves. In one of these subjects (the healthy boy), large slow waves appeared despite the fact that no increase in lung ventilation was noted. In this miscellaneous group, the effect of hyperventilation and exposure to low oxygen partial pressure were similar. The subjects who reacted with large slow waves to hyperventilation responded in the same way on exposure to low oxygen partial pressure, whereas those who did not react to hyperventilation with large slow waves did not respond to exposure to low oxygen partial pressure.

DISCUSSION

Does the 6–7 per second rhythm which occurs in the resting pattern of patients with Addison's disease represent a slower-than-normal *alpha rhythm*? Jasper and Andrews (7) have discussed a similar problem with respect to the slow rhythm which appears during sleep.

Several facts make it difficult to conceive that the slow rhythm in patients with Addison's disease constitutes a delayed alpha rhythm, i.e.:

(a) The predominance of the slow rhythm over the anterior part of the brain.

(b) The relatively weak reaction to vision. Rubin (8) observed in normal subjects that the precentral alpha rhythm responded as well to opening and closing of the eyes as did the occipital rhythm.

(c) The absence of speeding up of frequency immediately following closure of the eyes.

Features favoring the close relation of these two slow rhythms may be summarized as follows:

(a) The normal alpha rhythm may show at times a slightly lower frequency in the frontal region (7).

(b) An increase in period and amplitude of the alpha rhythm, especially over the frontal portion of the brain, has been shown by Jung (9) during periods of maximal relaxation and exhaustion.

(c) In normal subjects the large slow waves which develop during prolonged hyperventilation appear to arise from the frontal alpha rhythm. If the abnormality in the resting pattern of the electro-encephalogram of patients with Addison's disease represents an alpha rhythm which has been slowed down, then the unusual encephaloelectrical sensitivity which these patients exhibit to hyperventilation is readily explained.

What, if any, is the relationship between the abnormal slow rhythm of patients with Addison's disease and the slow frequency oscillations which occur in normal subjects during periods of drowsiness and sleep? The characteristic fatigue of patients with Addison's disease makes this question particularly pertinent. Two apparent differences between these two slow rhythms are known, i.e.:

1. The slow rhythm in Addison's disease is present when the patient is awake.

2. The pattern of the slow rhythm in most patients with Addison's disease is much more regular and pronounced than the random slow waves which are noted in normal subjects during drowsiness and sleep.

The lack of correlation between the abnormal slow activity during rest and the sensitivity to hyperventilation was difficult to explain. It is probable that the slow waves during rest facilitated the development of large slow waves during hyperventilation. However, since treatment (synthetic hormone) in some patients resulted in a decreased sensitivity to hyperventilation despite a persistence of, or an increase in, the abnormal resting pattern, it appeared that sensitivity to hyperventilation depended in part upon separate and additional factors.

It was apparent from the present study that restoration of blood pressure, plasma volume and electrolyte concentration prevented neither the occurrence of the electro-encephalographic abnormalities in the resting pattern, nor the sensitivity to hyperventilation.

The progression of the abnormal changes in the resting pattern of the electro-encephalogram in some patients during long continued desoxycorticosterone acetate therapy raises the question of whether or not synthetic hormone therapy may initiate or facilitate these changes. The fact that abnormalities were observed in two patients prior to any therapy and the fact that several patients have been treated for from one to 3 years with adequate quantities of desoxycorticosterone acetate without the appearance of abnormalities in the resting electro-encephalogram suggest that synthetic hormone therapy does not necessarily initiate the changes. Whether the progressive increase in electro-encephalographic changes which occurred in 3 patients during long continued desoxycorticosterone acetate treatment (one year or more) was facilitated by the synthetic hormone therapy cannot be stated at present.

Recently it has been shown that the administration of excessive doses of desoxycorticosterone acetate may result in a profound disturbance in the ratio of potassium to sodium in the tissues (10). Clinical evidence (11) as well as experimental evidence (12) of the development of paresis and paralysis of muscles of the extremities as the result of excessive desoxycorticosterone acetate therapy has been described. It is probable that overdosage of synthetic hormone with the resulting profound shift in sodium to potassium ratio in previously untreated patients with Addison's disease might induce detectable changes in the metabolism of brain tissue.

The occurrence of an abnormality in such a high proportion of patients who were in relatively good clinical condition suggests that

factors other than those which desoxycorticosterone acetate is known to correct are responsible for the changes. The one disturbance in this respect which immediately comes to mind is the regulating effect of the adrenal cortex on carbohydrate metabolism, since it has been shown that certain adrenal cortical factors, other than desoxycorticosterone, exert a pronounced effect upon carbohydrate metabolism (4). These factors are contained to some extent in the aqueous adrenal cortical extract, although their concentration in this extract is not high, and hence very large doses of extract must be employed to produce the carbohydrate regulating response. It is possible that if large doses of aqueous adrenal cortical extract (20–30 cc per day) could have been administered for a prolonged period (2–6 weeks) in the absence of desoxycorticosterone acetate, the abnormality in the resting pattern of the electro-encephalogram might have been modified. The very high cost of continuous aqueous adrenal cortical extract therapy precluded such a study.

On the basis of the studies of Engel and Margolin (3) it was thought that some correlation might exist between the presence of the abnormal resting pattern and the clinical and laboratory evidence of the extent to which the "carbohydrate defect" was present, since patients with Addison's disease appear to vary greatly in respect to the degree to which carbohydrate metabolism is disturbed (4). Thus far, no correlation has been shown in this respect since some patients with pronounced disturbance in carbohydrate metabolism failed to exhibit the abnormality in electro-encephalograms and since other patients in whom, according to our present tests, there was little or no evidence of disturbance in carbohydrate metabolism, had the characteristic abnormal slow rhythm.

Is the abnormality in the resting electro-encephalographic pattern (6–7 per second rhythm, which is larger and more regular over the anterior portion of the brain), which was observed in the majority of 25 patients with Addison's disease, pathognomonic of this disease? It may be stated that we have encountered similar pictures very rarely in adult patients studied in the Phipps Clinic laboratory, and pronounced only in a patient with Simmonds disease. However, several conditions are known to be associated with a slowing down of the general frequency:

Childhood. At one year of age 6–7 cycles per second is the typical

frequency (13, 14). However, this slow activity is a true slow alpha rhythm, with definite predominance in the occipital region and with the usual sensitivity to light.

Abnormality in blood constituents. Hypocapnia, hypoxia and hypoglycemia (15) slow down the frequency (6). Hypocapnia and hypoxia also induce larger potentials over the anterior portion of the brain.

Drowsiness and sleep, produce random slow waves (16). Maximal relaxation and exhaustion produce anterior predominance. However, the frequency is not slower than 8 per second (9).

Hypothyroidism. There is a definite relation between alpha frequency and metabolic rate (17) and bursts of slower waves in the frontal region have been reported (14) in hypothyroidism.

Epileptic patients sometimes show a larger, more regular rhythm over the anterior than over the posterior part of the brain—usually combined with a generalization of the tide of activity. Gibbs and Gibbs (6) have published records taken from epileptics with deterioration, which are somewhat similar to the electro-encephalograms of patients with Addison's disease. A 7 per second rhythm with anterior predominance has been observed in a few cases of severe epilepsy in our clinic. These abnormalities have usually persisted for only short sequences.

The tendency to develop large slow waves during hyperventilation is not at all specific for Addison's disease, but is seen in many other different conditions, such as in childhood, adolescence, hyperventilation, tetany and epilepsy.

SUMMARY

In 18 of 25 patients with Addison's disease (23 of whom were in relatively good clinical condition at the time of this study) definite abnormalities were observed in the resting pattern of the electro-encephalogram. These changes were characterized by:

1. The presence of oscillations which were slower than the normal alpha rhythm, which had a predilection for the frontal area of the cerebral cortex, and which were relatively refractory to the usual effect of opening the eyes.

2. An unusual sensitivity of the electro-encephalogram to voluntary hyperventilation.

3. A reduction in incidence of low voltage-high frequency activity (beta waves).

The abnormalities of the electro-encephalogram during rest may progress during therapy with synthetic hormone.

Treatment with desoxycorticosterone acetate, aqueous adrenal cortical hormone, crystalline components of the vitamin B complex and a diet high in readily available carbohydrate, failed to correct the abnormality of the resting pattern.

CONCLUSION

Abnormalities in the resting pattern of the electro-encephalogram and an increased sensitivity of the electro-encephalogram to voluntary hyperventilation were observed in a high proportion of patients with Addison's disease. The abnormalities in the resting pattern of the electro-encephalogram in patients with Addison's disease were typical, but cannot be considered to be pathognomonic. Progression of these abnormal changes may occur during therapy with the synthetic hormone. Treatment with desoxycorticosterone acetate, aqueous adrenal cortical extract or intravenous infusions of glucose did not correct the abnormality in the resting pattern. However, adrenal cortical extract therapy and intravenous infusion of glucose did, in some patients, effect a marked reduction in the sensitivity to hyperventilation.

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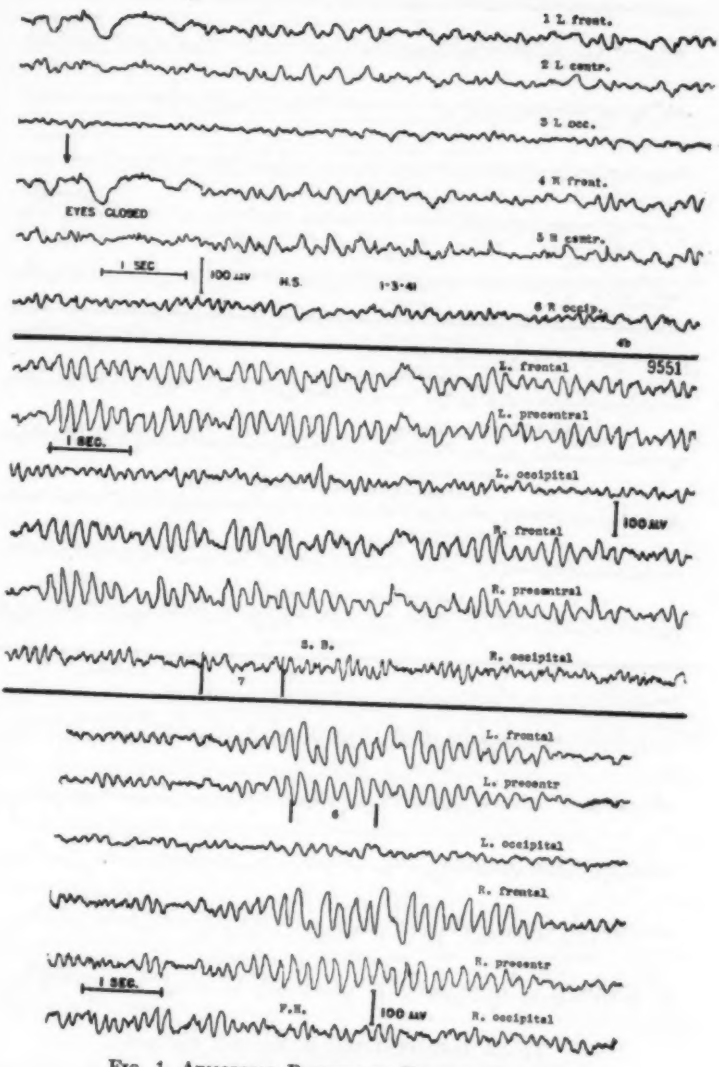

FIG. 1. ABNORMAL RHYTHM IN RESTING PATTERN

Note slow rhythm and frontal preponderance

Upper record: Patient H. S.
Middle record: Patient S. B.
Lower record: Patient F. H.

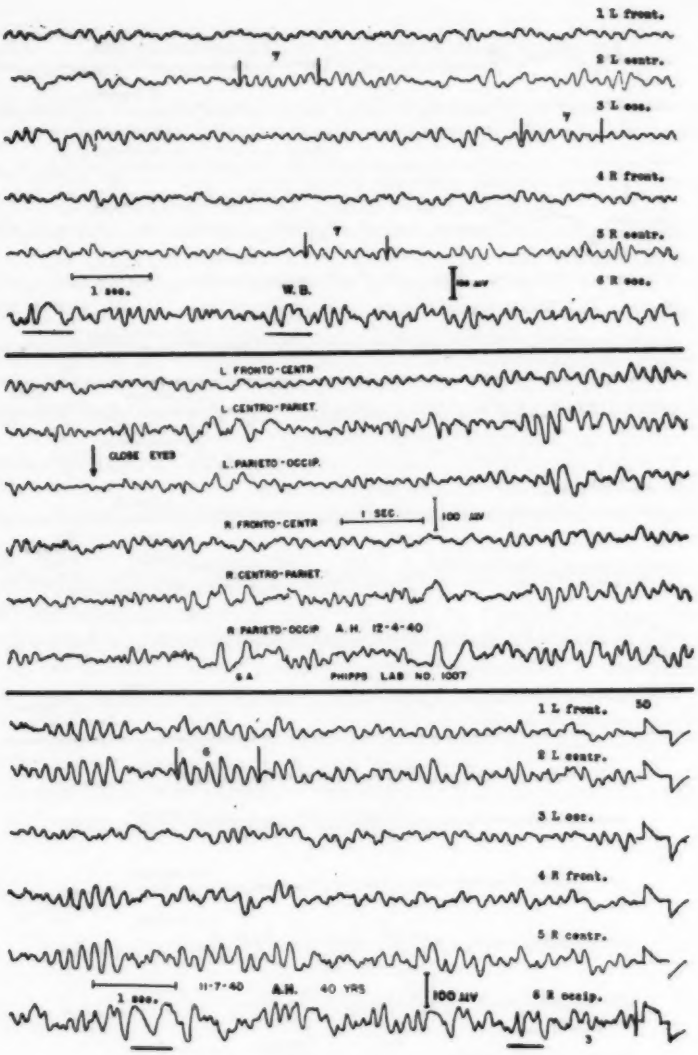

FIG. 2. IRREGULARITIES IN RESTING PATTERN

Upper record: Note occipital assymmetry and undeveloped spike-and-waves. Patient W. B.

Middle record: Note irregular larger and slower waves immediately after closing of eyes (sleep unlikely). Patient A. H., 40 years.

Lower record: Note irregular large slow waves in right occipital region. Patient A. H., 40 years.

The patients W. B. and A. H. had never shown any epileptic manifestations.

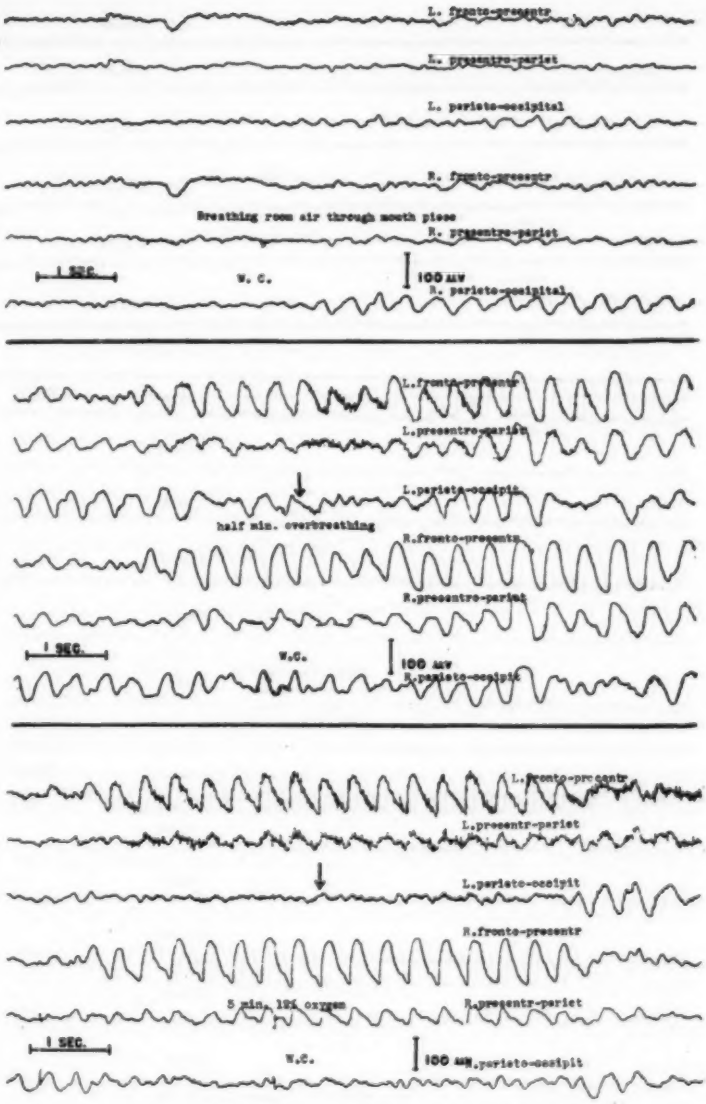

FIG. 3. EFFECT OF HYPERVENTILATION AND HYPOXIA

Three records from patient W. C.

Upper record: Resting pattern. Perhaps slight spontaneous overbreathing because of mouth piece. Respiratory volume 7.7 liters per minute.

Middle record: Effect of half a minute of voluntary hyperventilation.

Lower record: After five minutes spontaneous breathing 12% oxygen through mouth piece. Respiratory volume 6.7 liters per minute.

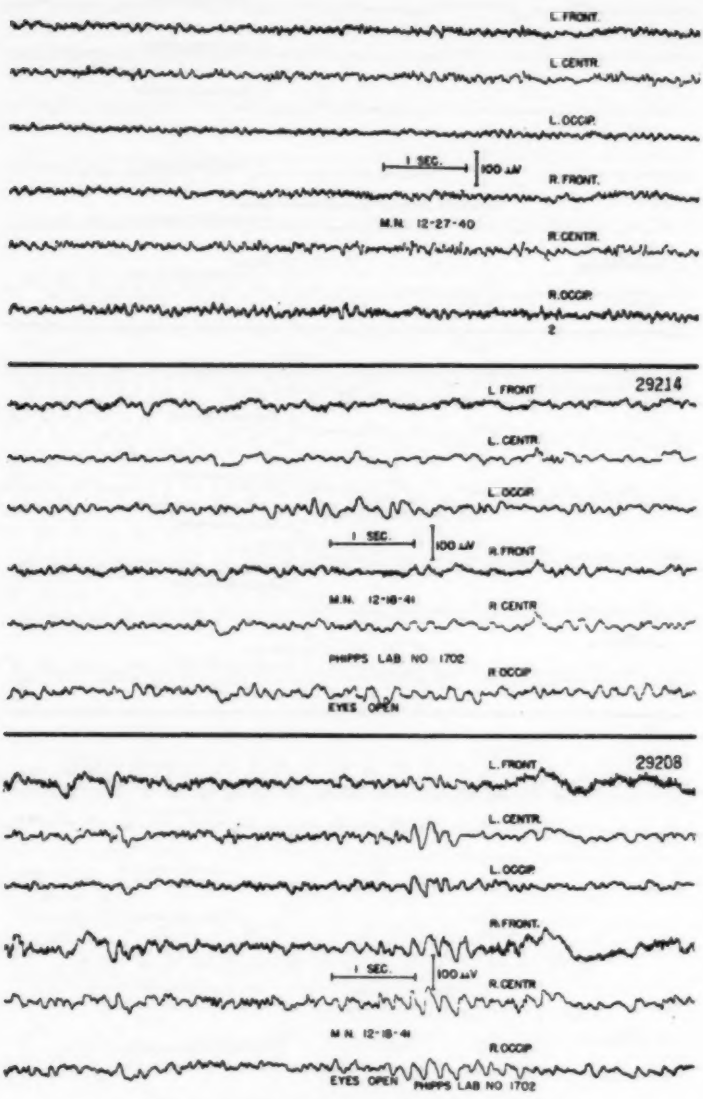

FIG. 4. APPEARANCE OF ABNORMALITIES IN RESTING PATTERN DURING DESOXYCORTICOSTERONE ACETATE TREATMENT

Three records from patient M. N.

Upper record: Before synthetic hormone treatment. Note abundance of beta activity.

Middle and Lower records: After treatment for one year with desoxycorticosterone acetate.

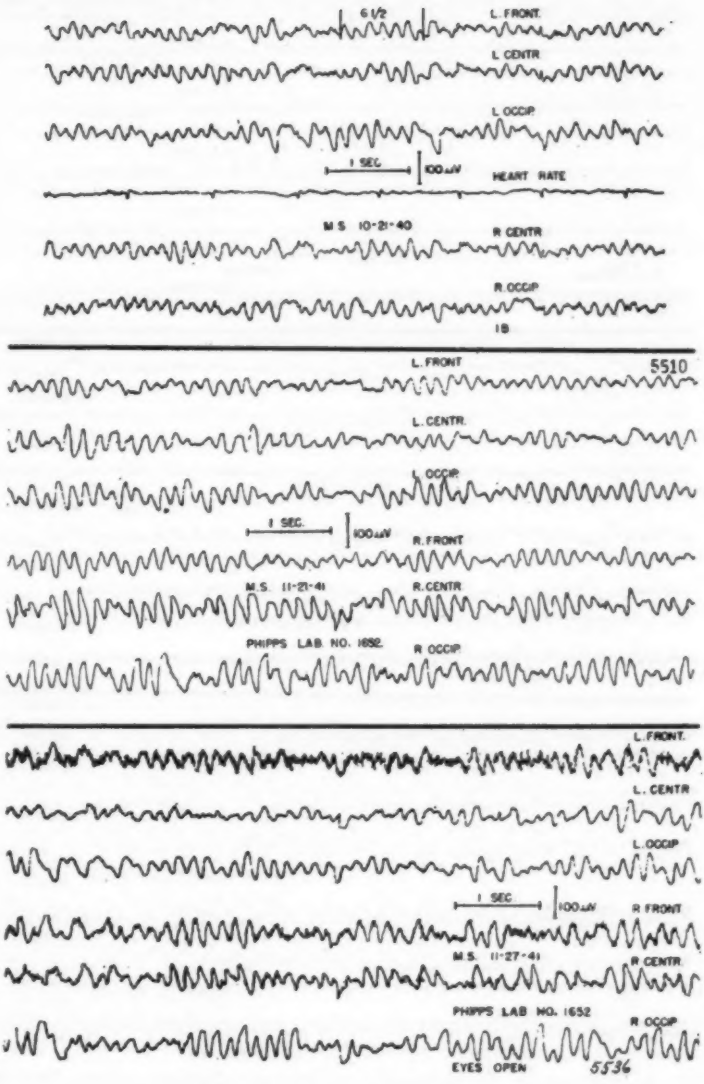

FIG. 5. INCREASE OF ABNORMALITIES IN RESTING PATTERN DURING DESOXYCORTICOSTERONE ACETATE TREATMENT

Three records from patient M. S.

Upper record: After treatment for 9 days with desoxycorticosterone acetate.
Middle and Lower records: After continuation of same treatment for one year.

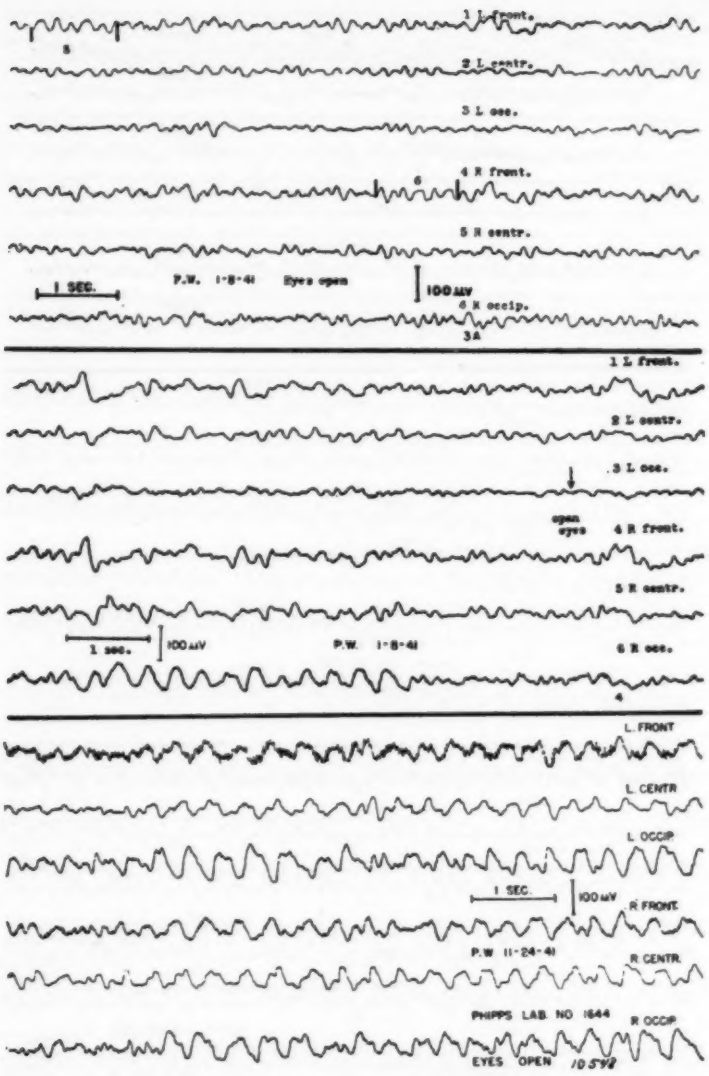

FIG. 6. INCREASE IN ABNORMALITIES IN RESTING PATTERN DURING DESOXYCORTICOSTERONE ACETATE TREATMENT

Three records from patient P. W.

Upper and Middle records: After treatment for 27 months with desoxycorticosterone acetate.

Lower record: After continuation of same treatment for one year.

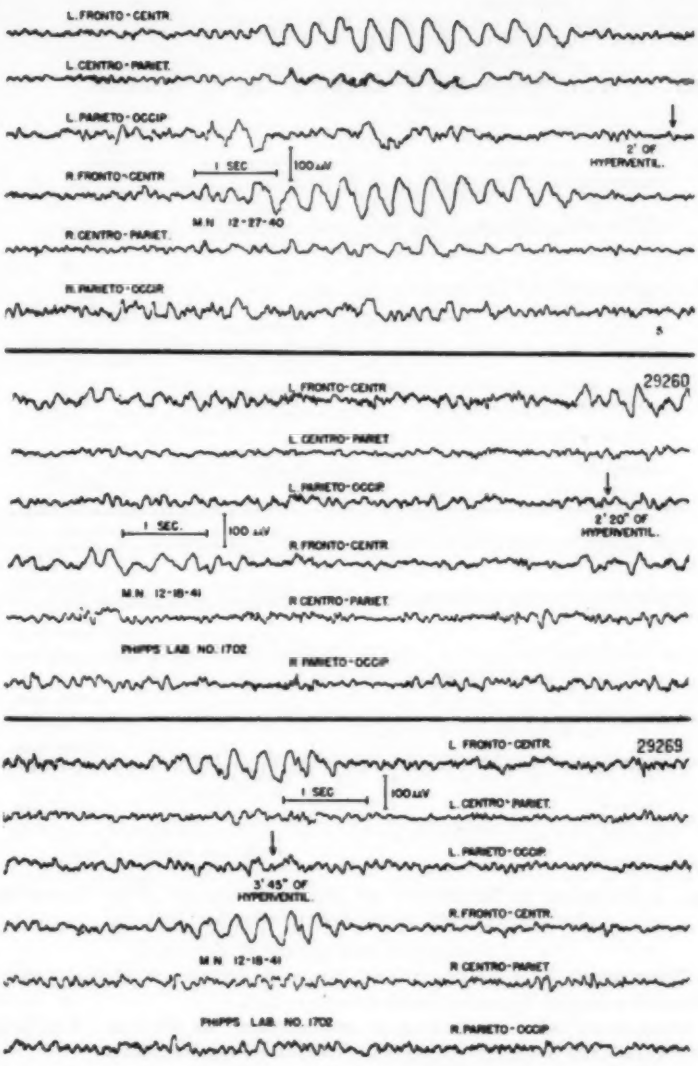

FIG. 7. DECREASE IN SENSITIVITY TO HYPERVENTILATION FOLLOWING TREATMENT WITH DESOXYCORTICOSTERONE ACETATE

Three records from patient M. N.

Upper record: Before synthetic hormone treatment. The effect of voluntary hyperventilation for 2 minutes.

Middle and Lower records: After treatment for one year with desoxycorticosterone acetate. The effect of voluntary hyperventilation for 2 minutes 20 seconds with first large slow waves after 3 minutes 45 seconds. Compare with Fig. 4 (same patient) the effect of treatment on the resting pattern.

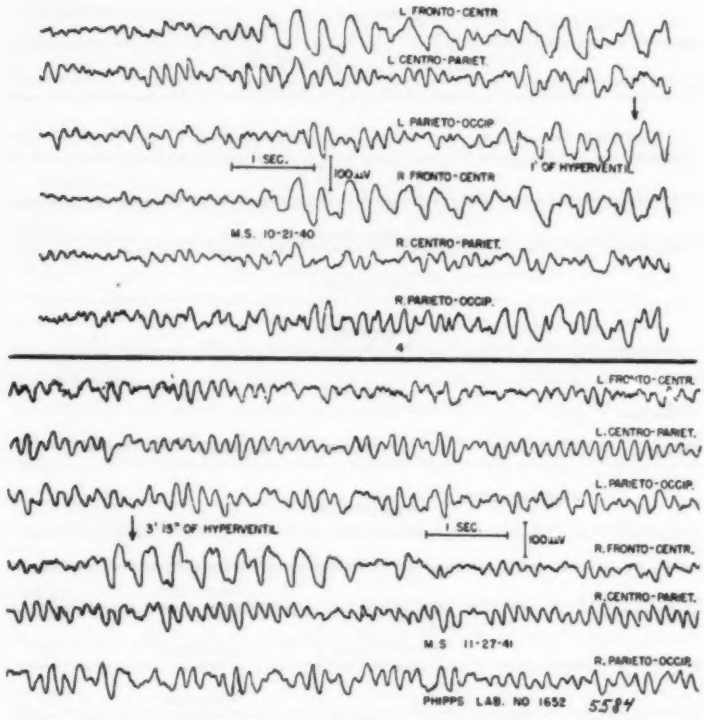

FIG. 8. DECREASE IN SENSITIVITY TO HYPERVENTILATION AFTER CONTINUED TREATMENT WITH DESOXYCORTICOSTERONE ACETATE

Two records from patient M. S.

Upper record: After treatment for 9 days with desoxycorticosterone acetate. Effect of voluntary hyperventilation for one minute.

Lower record: After continuation of same treatment for one year. First large slow waves after 3 minutes 15 seconds of voluntary hyperventilation.

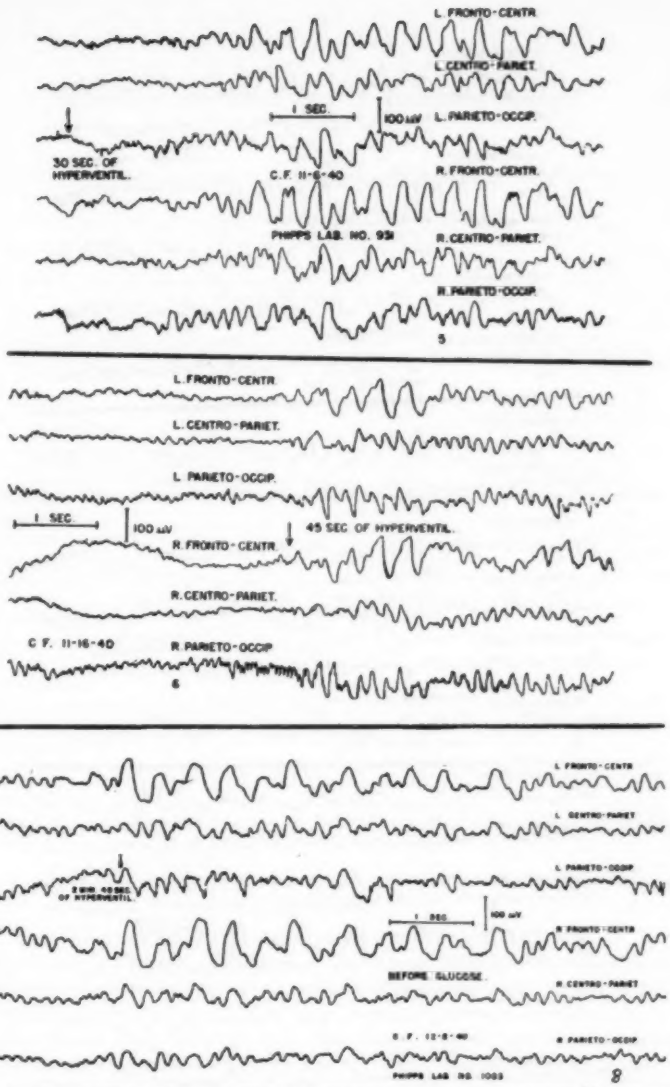

FIG. 9. DECREASE IN SENSITIVITY TO HYPERVENTILATION FOLLOWING TREATMENT WITH DESOXYCORTICOSTERONE ACETATE AND LATER WITH AQUEOUS ADRENAL EXTRACT PLUS VITAMIN B (SEE TEXT)

Three records from patient C. F.

Upper record: Before hormone treatment. In poor clinical condition. Large slow waves after 30 seconds of voluntary hyperventilation.

Middle record: After 10 days of treatment with desoxycorticosterone acetate. Better clinical condition.

Lower record: After 2 weeks further treatment with aqueous adrenal extract (4 cc. daily) plus vitamin B. First large slow waves after 2 minutes 40 seconds of voluntary hyperventilation.

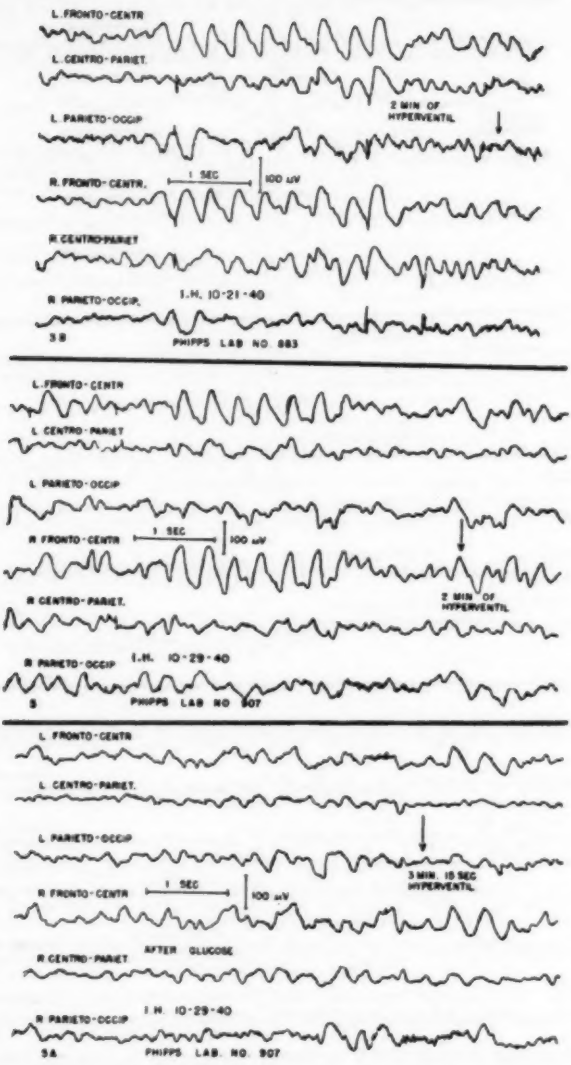

FIG. 10. DECREASE IN SENSITIVITY TO HYPERVENTILATION FOLLOWING GLUCOSE INJECTION

Three records from patient I. H. (after one year of treatment with synthetic hormone).

Upper and Middle record: Glucose not injected. Note constancy of the time of hyperventilation before the first runs of large slow waves appear.

Lower record: Immediately following intravenous injection of 10 gm. of glucose (same session as middle record).

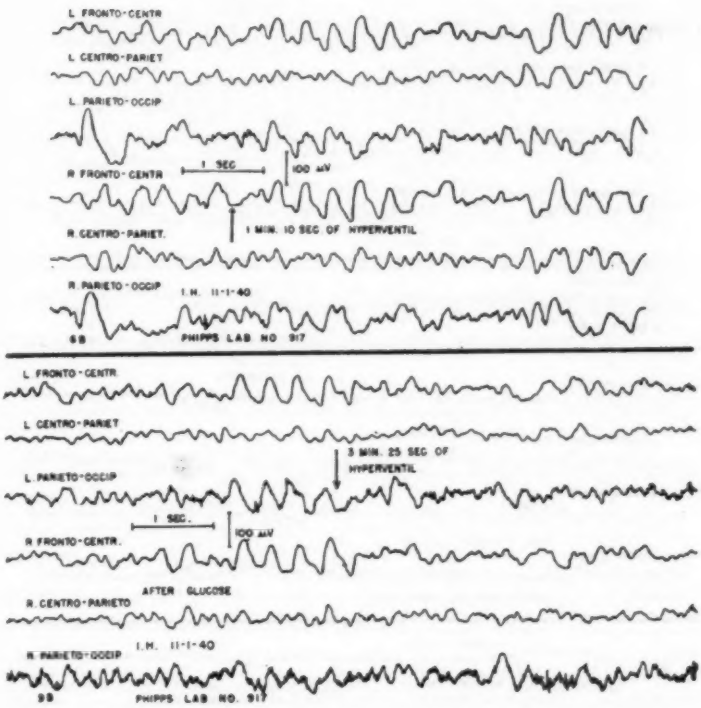

FIG. 11. DECREASE IN SENSITIVITY TO HYPERVENTILATION FOLLOWING GLUCOSE INJECTION

Two records from patient I. H. (same patient as in Fig. 10)

Upper record: Glucose not injected. First bursts of large slow waves during hyperventilation (treated with 40 cc. aqueous adrenal extract during last 24 hours in addition to synthetic hormone).

Lower record: First burst of large slow waves during hyperventilation immediately following intravenous injection of 10 gm. of glucose (same session as upper record).

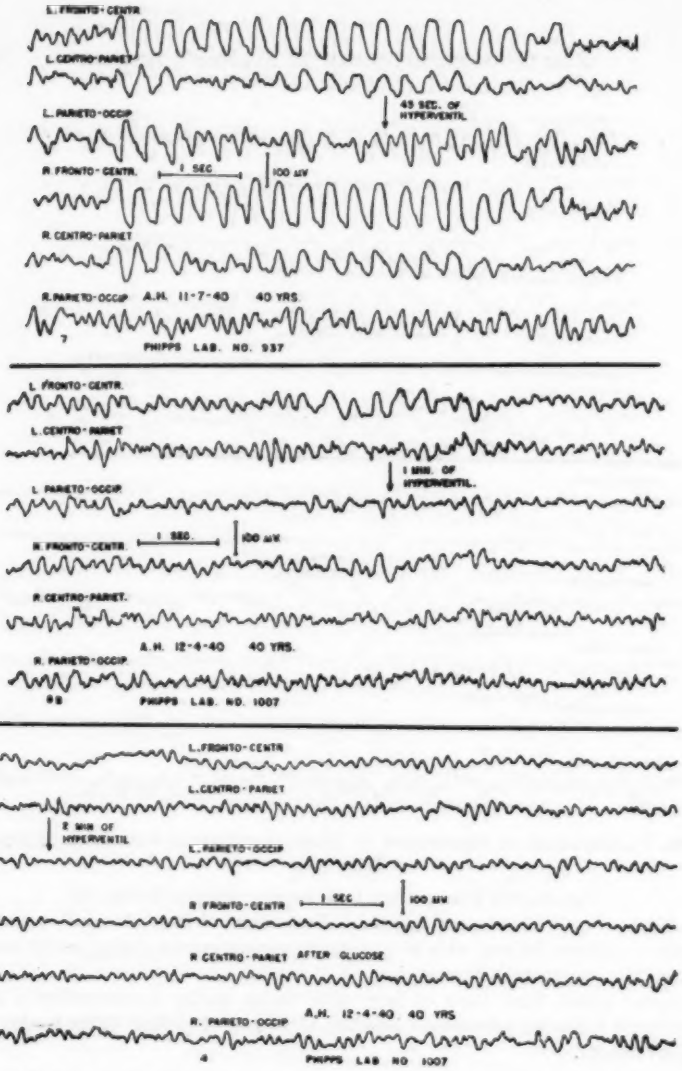

FIG. 12. DECREASE IN SENSITIVITY TO HYPERVENTILATION FOLLOWING GLUCOSE INJECTION

Three records from patient A. H.

Upper record: Glucose not injected (after treatment for 17 months with synthetic hormone).

Middle record: Glucose not injected (after treatment for 4 weeks with vitamin B (see text) and 5 cc. of aqueous adrenal extract daily in addition to synthetic hormone). End of voluntary hyperventilation.

Lower record: End of hyperventilation immediately following intravenous injection of 10 gm. of glucose (same session as middle record).

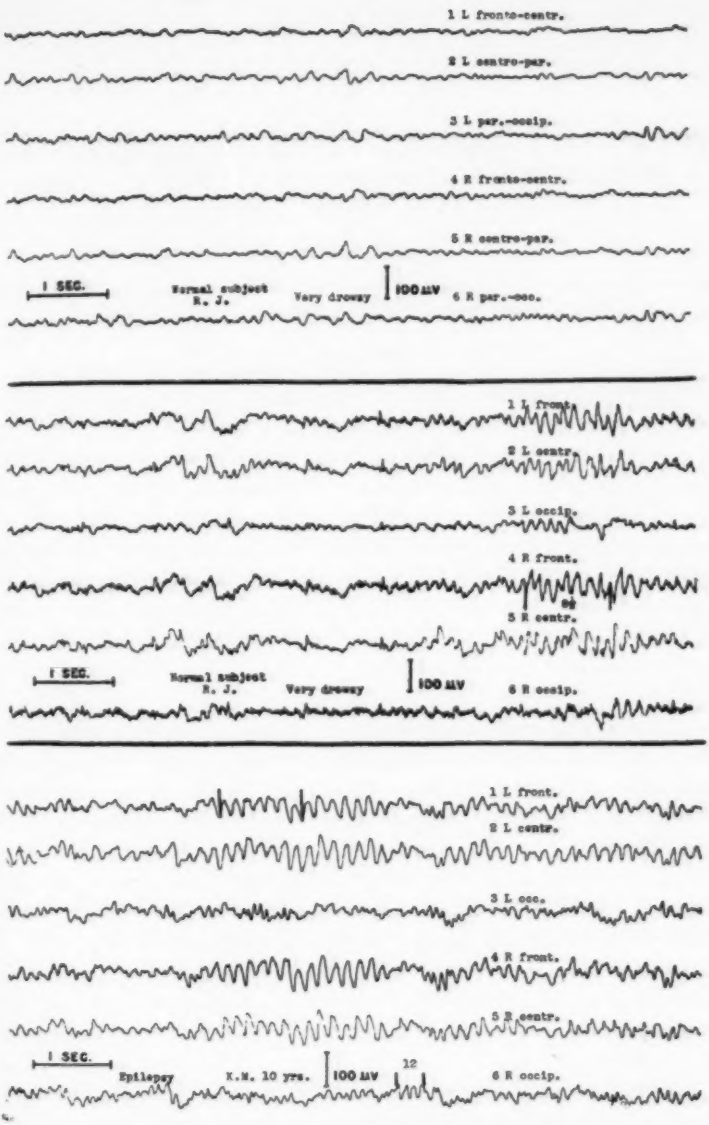

FIG. 13. RECORDS WITH SOME FEATURES IN COMMON WITH THE RECORDS FROM ADDISON PATIENTS, BUT OBTAINED FROM SUBJECTS NOT HAVING ADDISON'S DISEASE

Upper record: Healthy subject, drowsy. Note irregular pattern.

Middle record: Same subject, drowsy. Note frontal preponderance but 8½ per second frequency.

Lower record: Ten year old boy with epilepsy. Note 7 per second rhythm with frontal preponderance.

THE RELATION BETWEEN THE CHEMICAL STRUCTURE OF FATS AND THEIR ABILITY TO PRODUCE GASTRIC INHIBITION

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The observation that fats inhibit gastric digestion has been attributed to Aristotle (1). The first accurate report of this phenomenon, however, is that of Beaumont (2), who in 1833 prepared tables of the digestibility of various foods based on the length of time they remained in the stomach. In 1876 Zawilski (3) called attention to the delayed gastric emptying time caused by fat and a few years later Ewald and Boas (4) reported detailed observations on the inhibition by fat of gastric secretion. Since then the phenomena of gastric inhibition by fats have been studied by a number of physiologists, notably Pavlov and his pupils (5) and, more recently, Ivy (6), Lim (7) and their collaborators.

It is now well established that the ingestion of fat will inhibit both the motor and secretory mechanisms of the stomach. The secretory inhibition involves enzymes as well as acid; it affects chemical, mechanical and "psychic" secretion alike. It has been shown (8) that gastric inhibition by fat is dependent upon a humoral mechanism—an inhibitory hormone known as enterogastrone which is apparently released from the duodenal mucosa when neutral fat or fatty acids reach that region. A similar inhibitory principle known as urogastrone has been recovered from urine and may be identical with enterogastrone (9). Although purified extracts of enterogastrone and urogastrone have been made, the active principle or principles have not as yet been isolated.

Relatively little is known about the relation between the chemical structure of a fat and its ability to induce inhibition. Only a few workers have made comparative studies of different fats, and some of these studies have been inconclusive. Cannon (10) observed that pork fat left the stomach more rapidly than mutton fat or beef suet. Tönnis

and Never (11) studied a number of unsaturated oils but observed no striking differences between them. Badylkes, Einhorn and their collaborators (12) reported that margarine was less effective than butter in inhibiting secretion, but more effective in inhibiting motility. A critical examination of their data, however, indicates that the results were variable and the differences not impressive. McSwiney and Spurrell (13) failed to get gastric inhibition with mineral oil. Sherman (14) stated that the softer and more fluid the fat the more rapidly it would leave the stomach, but he did not give the sources of his information. Roberts (15), on the other hand, failed to find a relation between the physical properties of the fat and its inhibitory power; he found that the higher the iodine value, the greater was the inhibitory response. Wilder and Schlutz (16) reported a few observations made with saturated fats in which the length of the carbon chain was varied; the shorter the chain, the greater was the inhibition.

Our interest in this problem originated with some studies (17) in which one of us (H.C.T.) had been engaged in which it was found that the intestinal absorption of different fats bore a definite relation to their chemical structure. We were interested to find out whether a similar relation would hold between chemical structure and inhibitory power. If such were the case it might be assumed that absorption of at least a minimal amount of fat from the intestine rather than some purely mechanical effect of the fat was responsible for releasing the inhibitory mechanism. It was with this in mind that the present experiments were undertaken.

EXPERIMENTAL

Our first experiments were carried out on cats. Since the phenomena of gastric inhibition by fat are known to show both individual and familial variations (18) we attempted to use only a small number of animals, carrying out as many experiments as possible on each. After an overnight fast, the animals were given by stomach tube an artificial cream mixture made by homogenizing one or another type of fat in skim milk. Three hours after the administration of this test meal a stomach tube was again introduced and the contents removed, the stomach being washed several times with distilled water. The

acid in the combined stomach washings was titrated with N/10 NaOH as a measure of gastric secretion. The motility of the stomach was studied by extracting the fat from the stomach contents and determining what percentage of the fat introduced three hours before was still present. The results of experiments carried out on two cats are summarized in Table I. In each series the two types of fat were compared in the same animal.

It will be noted that in each set of experiments the change to a more unsaturated type of fat resulted in: (1) a reduction in gastric acidity; and, (2) a greater retention of fat in the stomach.

Similar studies were carried out on rats. Adult animals, fasted

TABLE I

Experiments on Cats

	TYPE OF FAT	QUANTITY INTRODUCED	NO. OF EXPERIMENTS	N/10 ACID IN STOMACH CONTENTS (AVERAGE)	PER CENT OF ORIGINAL FAT RETAINED IN STOMACH FOR 3 HRS. (AVERAGE)
		gms.		*cc.*	
Series I	Tripalmitin + tristearin (2:1)	7.5	3	13.8	25.6
	Olive oil	7.5	3	7.0	43.1
Series II	Butter	20	11	34.5	57.7
	Linseed oil	20	6	23.5	71.1

overnight, were given artificial cream mixtures by stomach tube, these creams being prepared by homogenizing various fats in skim milk. The quantity of fat administered in each case was 1 gram. The fat had been stained with Sudan III before homogenization, so that its progress through the digestive tract could be the more readily followed when the animals were sacrificed. Three hours after the administration of this test feeding the animals were sacrificed and the gastrointestinal tract was opened. The quantity of fat remaining in the stomach was determined gravimetrically after extraction, and the distance travelled by the stained fat along the intestine was noted. The observations on gastric retention in these rat experiments are summarized in Table II:

TABLE II

Experiments on Rats

TYPE OF FAT	IODINE VALUE	NO. OF EXPERIMENTS IN EACH GROUP	PER CENT OF INGESTED FAT RECOVERED FROM STOMACH AFTER 3 HRS. (AVERAGE)
Tripalmitin + tristearin (2:1)	2	10	61.9
Butter	32	10	68.0
Olive oil	83	10	71.2
Linseed oil	185	10	78.0

It may be noted that the more unsaturated fats tended to remain in the stomach. This finding is confirmed by the data showing the progress of the stained fat along the intestine, which are collected in Figure 1.

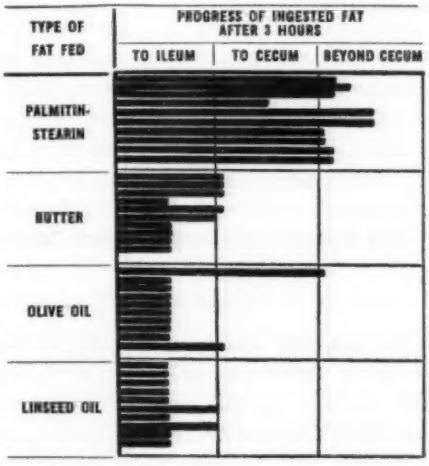

FIG. 1

The data indicate that the more saturated fats which show the least gastric inhibition and the least retention in the stomach tend to pass down farthest in the intestinal tract.

In order to determine whether such findings were valid for man a number of experiments were carried out on a convalescent infant from

the wards of the Harriet Lane Home. This infant was given a barium meal containing one or another type of fat—a tripalmitin-tristearin mixture, butter fat or olive oil. Following the administration of this test feeding, which was always given on an empty stomach, observations were made with the fluoroscope at frequent intervals, the time required for the last of the barium to leave the stomach being taken as a measure of the degree of motor inhibition caused by the fat. The results of eight such experiments are shown in Table III:

TABLE III

Human Subject

Emptying time of stomach as influenced by ingestion of different fats

FAT FED	EMPTYING TIME OF STOMACH (HRS.)
Tripalmitin + tristearin (2:1)	2½
	2
	2
	2
Butter fat	3½
	4½
	4¼
Olive oil	5¼

The data in this human experiment confirm those obtained with cats and rats.

COMMENT

Our findings on cats, rats and a human subject which have been presented above are in agreement with those of Roberts (15) in that gastric inhibition tends to increase with the iodine value of the administered fat although the relation between them is not a linear one. Linseed oil, for example, with an iodine value more than double that of olive oil causes only a small increase in gastric inhibition. When, however, we compare the available data on gastric inhibition by different fats with the intestinal absorption of these same fats, a striking parallelism is encountered. With saturated fats the effect of shortening the carbon chain is to increase absorption (17) and to increase gastric inhibition (16). With unsaturated fats the degree

of absorption seems to be determined not by the iodine value, but rather by the per cent of fatty acids containing one or more double bonds (17); the introduction of more than one double bond into a fat causes only a slight improvement in absorption. Our data and those of Roberts on the effect of various unsaturated fats upon gastric inhibition suggest strongly that a similar relationship holds between the structure of the fat and this function as well. Finally, we may mention the fact that splitting is a prerequisite for fat absorption and seems likewise to be necessary to produce gastric inhibition. Ethyl esters have been found by us to be split with difficulty, and similarly Roberts has found difficulty in demonstrating gastric inhibition with ethyl oleate.

From the foregoing evidence we are led to conclude that the phenomena of gastric inhibition are precipitated by absorption of some fat from the upper intestine, presumably followed by the liberation of enterogastrone, rather than by any physical property of the fat itself.

The relation between motor inhibition and fat absorption has been noted by other workers (19) who have maintained that the rate of discharge of a fat from the stomach was the factor controlling its absorption, only fats causing marked inhibition being discharged slowly enough to permit relatively complete absorption. This explanation scarcely seems tenable, however, in view of the extensive evidence now available (20) that passage of fat into the duodenum is a prerequisite for fat inhibition.

The purpose of the gastric inhibitory mechanism remains obscure, although a number of possibilities have been suggested. According to one view the inhibition of gastric motility serves the purpose of permitting the fat to enter the intestine no more rapidly than it can be absorbed. In support of this are the experiments of Emery (21), who found fat absorption normal in gastrectomized dogs only when the food was administered so slowly that the fat entered the duodenum at the approximate rate at which it normally leaves the stomach.

According to Sherman (22) the motor inhibition serves the purpose of preventing hunger. He calls attention to the difficulties experienced by the German troops during the first World War when a scarcity of fats prevailed. Owing to the rapid emptying of the stomach hunger pains made their appearance relatively soon after a meal was eaten.

The function of the secretory inhibition is less easily explained. It has been suggested (23) that the more rapid discharge of acid into the duodenum, such as might occur in the absence of fat in the diet, might make it difficult to maintain the alkalinity of the duodenal contents needed for the optimal function of the pancreatic enzymes. As far as we are aware no one has suggested a reason for the inhibition of gastric enzymes caused by fat.

CONCLUSIONS

Experiments in animals and in a human subject indicate that the gastric inhibitory response to fat varies with the chemical composition of the fat. There is a striking parallelism between the ease of absorption of a fat and its ability to produce gastric inhibition, which suggests that absorption of some fat from the duodenum is a prerequisite for the liberation of enterogastrone.

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THE ISOLATION AND IDENTIFICATION OF THE GONOCOCCUS*,[1]

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The culturing of the gonococcus from clinical material has been recommended by several investigators, and its reliability and superiority over the smear technic alone has been confirmed by many others (1) (2) (3) (4) (5) (6). Nevertheless, there seems to be a tendency to rely upon smears alone for laboratory diagnosis of gonococcal infections because of real and fancied difficulties to be encountered in the cultural method. There can be little doubt that greater accuracy in laboratory diagnosis of gonococcus infections is attained when the culture method is combined with the smear technic. This is especially true in cases treated with sulfonamide compounds (7) (5).

During 1940 nearly 3000 cervical and vaginal specimens from patients with acute, subacute, or chronic gonococcal infections of the urogenital tract, all of whom received treatment with one of the sulfonamide drugs after diagnosis was established, were examined by smear, culture, and in some instances, by a complement-fixation test for gonococcus infection. Smears and cultures were taken before, during, and after treatment was completed. The technics used, for the most part, were those of Carpenter and his associates, although some modifications of our own were introduced. Because of the simplicity of the culture method and its superiority over the smear technic alone, we offer our methods and comment on some of our observations and experiences.

2,704 specimens from 1571 patients were examined, the number of cultures taken from a single patient varying from one to 23. These specimens were taken from each patient admitted to the dis-

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pensary during the period of this study. 322 of the 2704 specimens were positive by culture or smear. Of the total positive specimens, 39 (12.1 per cent) were positive by smear only; 209 (64.9 per cent) were positive by culture only; 74 (23 per cent) were positive by both smear and culture. Grouping the results differently it is obvious that 35.1 per cent were positive by smear and 87.9 per cent were positive by culture. These figures indicate that in the presence of gonococci in the cervix, the chance of discovering them is about 2½ times as great by culture as it is by smear. It is a common and almost constant experience to find smear and culture positive in the first examination of a recently infected woman, and to find the smear negative and culture positive on the third to fifth day after treatment with sulfanilamide, sulfathiazole, or sulfapyridine.

The technic evolved prior to the commencement of the study being reported, proved quite satisfactory. Modifications of previously published methods were used, but for the convenience of the reader, we give our methods in some detail, especially since it has been observed that some workers experience considerable difficulty with the culture method.

Specimens were taken by the clinician on a sterile swab through a speculum (where indicated) *without* lubricant. The swab was first *rolled* on a sterile slide (to avoid introducing contaminants into the culture medium), then the same swab was introduced into a tube of semi-solid medium and placed into an incubator at 36°C. until taken to the laboratory. The smears were stained by Nicholle's modification (8) of the Gram stain. Other staining technics were used at times, but for convenience and accuracy, the Nicholle's method was generally used. Burke's modification (9) of the Gram stain was used with equally satisfactory results and the differential stain of Walton (10) was used for a time on duplicate slides. The slides were examined carefully; no smear was reported as negative without having been examined for at least 5 minutes. Many slides were prepared in duplicate and examined by two or more persons.

After smearing slides, the swabs were placed into semi-solid medium made by Raven's formula (11) or more recently with a dextrose-starch medium of the following composition:[2]

[2] This medium is only slightly modified Difco Dextrose-Starch agar.

Peptone (Proteose peptone #3 or Nutri peptone)	15. gms.
Dextrose	2. gms.
Soluble starch	10. gms.
NaCl	5. gms.
Di-sodium phosphate	3. gms.
Gelatin	10. gms.
Agar agar	4. gms.
Distilled water	1000 cc.

Adjust to final pH 7.4. Sterilize by usual method in autoclave.

These two media gave equally satisfactory results. The medium with swab immersed was placed into an incubator at approximately 36°C. and held for a few hours, not more than 12. A series of experiments showed that good results could be obtained when the swabs were allowed to remain in this medium up to 12 hours, but fewer isolations were obtained when the swabs were held in the semi-solid medium for 24 hours or longer, and no isolations were made when plates were not streaked within 48 hours. Triplicate swabs taken from the same patients were held in the semi-solid medium at 36°C., room temperature and in the refrigerator. Before 12 hours, equally satisfactory isolations were made from swabs held at incubator and refrigerator temperature. After 24 hours, specimens held at incubator temperature were more likely to give positive isolations than those held in the refrigerator. Swabs held in semi-solid media at room temperature were quite frequently found negative for the gonococcus after two or three hours. This observation is understandable, since at body temperature the gonococcus has as good a chance to grow as have contaminating organisms. Likewise, at refrigerator temperature, the contaminants and the gonococcus are restrained equally. At room temperature the contaminating organisms quickly outgrow the pathogen. For our work we continue to hold specimens at incubator temperature.

After the publication by Woods (12) on p-aminobenzoic acid and its "neutralizing" effect on sulfanilamide, the addition of this substance to our medium was considered because many of the patients from whom our specimens were taken were receiving a sulfonamide drug. Discussion with Dr. E. K. Marshall, however, indicated that it was improbable that the addition of p-aminobenzoic acid would be neces-

sary, since a substance which acts similarly is present in body fluids and in peptones used in the media. A few trials were made in which p-aminobenzoic acid was added to the media, but plates containing this compound yielded no more gonococcus isolations than did control plates without p-aminobenzoic acid. It seemed, then, that no inhibiting sulfonamide was being carried into the medium with the specimen, or that the medium as routinely prepared contained some substance which acted like p-aminobenzoic acid in checking the sulfonamide activity *in vitro*.

Within a few hours after collection from the patient, the specimen was taken to the laboratory, being kept warm in transit by placement in a water jacketed warm chamber or vest pocket. At the laboratory the specimen was streaked on chocolate agar plates.

At the time this work was first begun in our laboratory, Douglas Medium (13) was the accepted base for the chocolate agar. However, we utilized the basic agar at hand, pork infusion, and the results were so satisfactory that its use has been continued. Recently Carpenter and others (5) (7) have reported on the use of a dehydrated medium containing a dehydrated hemoglobin marketed by Difco, which gives satisfactory results and places the medium within reach of the smaller laboratory or even the field laboratory with a minimum of equipment. We have also successfully used Dextrose-Starch agar (Difco), containing heated blood, in a short series of cases.

Since the type of peptone to be used in media for the isolation of the gonococcus is so emphatically stressed by some workers, our basic media were made with a number of different peptones for purposes of comparison. Those compared were:

A. Pancreatic digest of casein (Armour)
B. Peptic digest of pork (Leifson)
C. Pancreatic digest of beef (Wilson)
D. Proteose peptone #3 (Difco)
E. Tryptone (Difco)
F. Medo peptone (Wilson)

All media contained, in addition to a 2 per cent concentration of peptone, 0.05 per cent dextrose, 0.5 per cent NaCl, disodium phosphate 0.5 per cent and agar 1.5 per cent. The pH was adjusted to 7.4 and 10 per cent citrated human blood was added to the heated medium.

Multiple specimens were streaked on plates containing each of the above media. Growth of the gonococcus was obtained on all media regardless of the type of peptone used, but more satisfactory results were obtained with regard to size of colonies and rapidity of growth when using peptones C, D and F in the order named. Peptones A, B, and E are not recommended on the basis of this experiment. As a result of this experiment, we have used Proteose peptone #3 or Nutri peptone[3] (Wilson) in the media for this study. The formula for chocolate agar used routinely was as follows:

Pork infusion base 1000 cc. (Made by infusing 10 Kg. finely ground pork trimmings in 20 Kg. distilled water for 1 hour and boiling for 5 minutes, stirring constantly while heating. Strained through gauze and coarse filter paper.)

Peptone (Nutri peptone or Proteose peptone #3)..... 10. gms.
NaCl..... 5. gms.

Dissolve with heat, adjust to pH 7.6, boil for 20–30 minutes, restore volume of water lost by addition of distilled water. Add:

Agar agar..... 15. gms.

Dissolve by heating, check reaction, allow to sediment, remove precipitate, melt in Arnold sterilizer, dispense into tubes or flasks, and sterilize in autoclave for 15–20 minutes at 15 pounds pressure. When ready for use, 10 per cent citrated or defibrinated human, horse, or rabbit blood is added to the melted medium at a temperature of 80–90°C. and rotated gently to avoid bubbles until chocolate-like appearance is obtained. Dispense into sterile petri dishes. (We have routinely made use of citrated human blood obtained from reagin-containing blood at the hospital blood bank.)

Plates were streaked by rotating the swab from the semi-solid medium on the surface of about $\frac{1}{3}$ of a chocolate agar plate. With a platinum loop, streaks were made by drawing the inoculum at right angles to the inoculation over the balance of the plate. By this method there were rarely positive plates on which isolated gonococcus colonies were not present.

The plates were then placed into a suitable receptacle (museum jar) equipped with one inlet in the lid. (It is important that moisture be present during incubation so a sponge of wet gauze was placed on the

[3] Nutri peptone was used in the basic medium at first and gave highly satisfactory results throughout these studies. Nutri peptone is a mixture of Medo peptone and Thio peptone. The former is understood to be a tryptic digest of casein and the latter a peptic digest of lung tissue.

bottom of each jar). The lids were sealed to the jar with a "rope" of "Plasticine." By means of a T tube the jar was connected to an exhaust pump equipped with manometer and to a tank of compressed carbon dioxide. Air was evacuated until the mercury in the manometer reached a height of 8 centimeters. Gas was then introduced into the jar until a negative pressure of 1 cm. mercury remained. The opening was then clamped off and the jars were incubated at 36°C. for 24–48 hours. Other methods (5) (14) for reducing oxygen tension and increasing carbon dioxide concentration have been suggested. One in which a lighted candle is placed in the jar and allowed to burn out after closure of the jar is particularly suitable for a laboratory with limited facilities and gives satisfactory results.

Examination of plates for gonococcus colonies was made after 24 and 48 hours of incubation. Plates were frequently positive after 24 hours' incubation in CO_2, but occasionally plates that appeared negative at the end of the first day's incubation in CO_2 were positive after an additional 24 hours' incubation under atmospheric conditions. It is interesting to note that carbon dioxide was not necessary for the continuation of growth in these cases.

Gonococcus colonies could usually be recognized by inspection of the plates. Suspected colonies were smeared and stained. If typical Gram negative diplococci were found, the colonies were fished to chocolate agar or dextrose-starch agar slants and incubated in an atmosphere containing CO_2. After growth had appeared on the slants, the species of Neisseria were identified by inoculation of dextrose, sucrose, and maltose semi-solid media. The gonococcus ferments dextrose only; the meningococcus ferments dextrose and maltose; *N. sicca* ferments all three of these sugars and *N. catarrhalis* ferments none (2). The tubes of semi-solid differential media were incubated under normal atmospheric oxygen, since the carbonic acid in a CO_2 jar causes the indicator to change color. All tubes incubated under CO_2 are acid and must be allowed to remain in normal atmosphere for a day or more to determine actual fermentation of the sugar.

The semi-solid medium used for differentiation had this formula:

1000 cc. single strength veal infusion
10 grams peptone (Nutri or Proteose peptone)
5. grams NaCl
4. grams Agar agar

Heat, clarify and adjust the reaction to pH 7.4
Add:
5.0 cc. Phenol red (0.2 per cent aqueous solution with 20 per cent ethyl alcohol)
Pour into flasks in exactly 100 cc. amounts and sterilize in the autoclave.

Before use, add aseptically 10–20 per cent sterile ascitic fluid and 0.5 per cent of the desired sugar which is previously sterilized in 5–10 per cent concentration in aqueous solution under vaseline. The ascitic fluid is collected aseptically and tested for sterility and must be inactivated by heating at 56°C. for one hour. Non-sterile ascitic fluid may be sterilized by heat without destroying its usefulness in media to be used for gonococcus cultivation (5). The medium is tubed aseptically in 4–5 cc. amounts.

The identification of gonococcus colonies, especially in plates containing a large number of contaminating organisms, is facilitated by the use of an indicator as reported by McLeod and others (15) (16). We have used p-dimethyl aniline monohydrochloride as the indicator dye; it is less expensive than the tetravalent dye first suggested. A solution of approximately 1.0 per cent of the powdered reagent is made in tap or distilled water and is ready for use after standing for 5 to 10 minutes. The reagent must be prepared daily to yield satisfactory results. When covered with this reagent, the Neisseria colonies turn red, then black within a few minutes. The organisms are still viable while the colonies are red, but are not likely to be living when the colonies have turned black. Some other bacterial colonies also change color in the presence of this reagent, but the colonies of such types can usually be distinguished readily from those of a Neisseria species. Some such organisms are listed by Thompson (17).

SUMMARY

By the use of the methods described in this paper, highly satisfactory results have been obtained in the cultivation of gonococci from urogenital tract infections. The methods described are comparatively simple, quick, and inexpensive. Two and one-half times as many specimens were positive by culture as by smear, and a more accurate check on the effectiveness of drug therapy was obtained. The results, however, indicate that some cases in which positive smears are obtained may be negative in culture due to excessive contamination or other reasons. It is therefore considered proper practice to combine both methods for the greatest possible accuracy.

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ORAL TREATMENT OF HAY FEVER WITH RAGWEED POLLEN

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The oral treatment of pollen hay fever is not a new idea. As early as 1900, some years before the introduction of the now well-established hypodermic form of therapy, Curtis reported good results in several patients treated with ragweed extracts by mouth. The next report on the method, however, was not until 1922, when Touart published his findings. Since that time there has been an increasing number of reports from various parts of the country. The exact method of treatment and the results have varied widely. Because of that great variation it was considered to be worthwhile to study another group of patients treated orally according to a standard plan with a commercially available preparation of ragweed pollen, in an attempt to determine more definitely the value of this form of treatment.

The results reported by other writers who have used the oral method of treatment are summarized in Table I. In general the results from hypodermic treatment were felt to be better than those from the oral form. McGrew, Schwartz, and Stier and Hollister worked with various pollens found in the west and south, but not with ragweed. London treated 42 patients with a combination of oral and hypodermic treatment and felt that the results were similar to those obtained when the hypodermic form alone was used. Most of the writers who have used the oral method of desensitization to ragweed pollen have reported a rather high incidence of reactions, chiefly gastro-intestinal in nature.

Some experimental work has been done by various workers in an attempt to determine the effect of gastric digestion on ragweed pollen, and the results here too have varied widely. Thiberge found that gastric digestion produced a definite reduction in the activity of pollen, while Bernstein and Kirsner were unable to demonstrate any appreciable decrease. Pollen administered orally failed to produce reactions in previously prepared passive transfer sites, according to

reports by Bernstein and Kirsner, Bernstein and Feinberg, London, and Zeller.

The present study was carried out during the summer of 1940. Eighty-two patients were treated with ragweed pollen administered orally, the preparation used being Lilly's Panoral—capsules of dried whole pollen mixed with starch. Eight more patients who were started on treatment are not included in the figures because of failure to follow instructions or to make final reports. Sixty-two (75.6 per cent) of the patients were treated pre-seasonally, and 20 (24.4 per cent) co-seasonally. In almost all cases the dose was started at 500 Noon units and increased according to a definite schedule until daily totals varying from 60,000 (at the 16th dose) to 240,000 units were reached. In a few cases, because of recent injection treatments or low skin sensitivity, the initial dose was somewhat higher—1500 to 8000 units. The dose was given soon after a meal, two or three times a week pre-seasonally and increased to daily with the onset of symptoms. The patients treated co-seasonally were treated daily or, in a few cases, three times a day until the maximum dose was reached.

TABLE I

Review of the literature—clinical results

Pollen-sensitive patients treated orally

AUTHOR	NO. PATIENTS	IMPROVED	SLIGHT OR NO IMPROVEMENT	REACTIONS
Curtis	8	8	0	
Touart	6	4	2	
Black	91	67	24	
McGrew	33	29	4	
Stier and Hollister	383	303	80	Some
Bohner	21	13	8	2
Rockwell	182	115	67	c. 10%
Bernstein and Feinberg	20	2	18	7
Black	40	16	24	
Zeller	22 oral	9	13	18 G.-I.
	20 comb. oral and hypo.	15	5	13 Nervous 20 Hay fever
Schwartz	65	57	8	Some
Alperstein	50	27	23	34
Feinberg et al.	141	42	99	33%

The results of this treatment are shown in Table II. Of the 62 patients treated pre-seasonally 3 (4.8 per cent) obtained practically complete relief of symptoms, 10 (16.1 per cent) good relief, and 25 (40.3 per cent) fair results. Twenty-one patients failed to be helped and 3 (4.8 per cent) stopped treatment because of reactions. None of the 20 patients treated co-seasonally received excellent or good relief, 14 (70 per cent) were mildly benefited, 4 (20 per cent) obtained no relief, and 2 (10 per cent) stopped treatment. Thus a total of 52 patients (63.4 per cent) were somewhat benefited, 25 patients (30.5 per cent) failed to obtain any relief, and 5 (6.1 per cent) stopped treatment because of reactions. A group of 37 patients (treated perennially or pre-seasonally) who received hypodermic treatment

TABLE II

Results of treatment with ragweed pollen: comparison of oral and hypodermic methods

TYPE OF TREATMENT	NO.	EXCELLENT		GOOD		FAIR		FAILURE		STOPPED TREATMENT	
		No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Oral											
Preseasonal	62	3	4.8	10	16.1	25	40.3	21	33.9	3	4.8
Co-seasonal	20	0	0	0	0	14	70.0	4	20.0	2	10.0
Totals	82	3	3.7	10	12.1	39	47.6	25	30.5	5	6.1
Hypodermic	37	13	35.1	11	29.7	9	24.3	4	10.8	0	0

during the same season gave distinctly better results. Thirteen (35.1 per cent) of them are classed as excellent, 11 (29.7 per cent) as good, 9 (24.3 per cent) as fair, and only 4 patients (10.8 per cent) failed to obtain any benefit.

In a study of this sort, the results must necessarily be based largely upon subjective reports, and it is difficult to establish any absolute criteria of different degrees of improvement. An attempt has been made here to weigh the reports of the patient against personal observations made by the physician at weekly or near-weekly visits. The term *excellent* is used for those cases in which the patient was essentially free of symptoms, with no more than an occasional sneeze or possibly very slight itching of the nose or palate. *Good* results were reported

when the patient was subjectively much better than he had been previously, and when the symptoms were never disabling or so severe as to interfere appreciably with sleep. These patients had frequent days free of all symptoms, and at no time had very severe symptoms. The patients who obtained *fair* relief felt that they were somewhat better than they had been previously, but continued to have some symptoms daily, and in many cases had a few severe attacks.

Since some of the patients in the orally treated group had had previous injection therapy an attempt was made to compare results with the two forms of treatment in these cases. Sixteen patients (19.5 per cent) received hypodermic treatment in 1939 (some of them having been treated also in previous years) and 13 (15.9 per cent) had had injections at some previous time but not in 1939. A few of

TABLE III

Comparison of oral treatment with previous injection treatment in the same patients

PREVIOUS YEARS	EXCELLENT				GOOD				FAIR				FAILURE			
Injections	3				8				9				9			
1940	EXC.	GOOD	FAIR	FAIL.	EXC.	GOOD	FAIR	FAIL.	EXC.	GOOD	FAIR	FAIL.	EXC.	GOOD	FAIR	FAIL.
Oral			2	1		1	4	3		2	6	1		1		8

these patients had had systemic reactions on injection therapy, one having forced to stop the treatment. Table III shows the comparative results with the two forms of treatment. In general the oral treatment gave less benefit than the hypodermic. All but one of the patients who had failed to obtain relief on injection therapy also failed on the oral. That one patient had received 16 injections from her local doctor without previous skin testing, and the exact nature of her treatment is not known. It might be noted that of the three patients whose improvement on oral treatment was excellent, two had had no previous treatment, and one had been for two years on oral therapy, also with good results.

One aspect of the oral form of treatment which has been the subject of considerable discussion is the matter of reactions. In our series reactions occurred in 33 patients (40.2 per cent). General systemic

reactions, other than respiratory, were experienced by three patients. One had a moderate urticaria after her first 60,000 unit dose, but after dosage was reduced and then increased again gradually she was able to take the same dose without difficulty. Another patient complained of itching with redness and roughness of skin over the arms and legs, as well as some sneezing and itching of the palate. These symptoms occurred two or three times early in the course of treatment, but did not interfere with the patient's following the schedule to a total of 120,000 units daily. The third case had some flushing and burning of the face, headache and swelling of the lips after each of the first three doses. This patient, a middle-aged woman with a history of previous stomach trouble, also had some gastro-intestinal discomfort and stopped the treatment because of that. A fourth patient stopped treatment on the advice of another doctor because of an attack of migraine which came on about seven hours after a dose of 60,000 units. Because she had been having similar attacks at approximately regular intervals it was felt that this one was probably not a reaction to the hay fever treatment. Six patients (7.3 per cent) reported very mild hay fever symptoms at intervals during the treatment, and one had a slight tightness suggestive of asthma after the first two doses only. In this connection it might be added that not only were there no definite cases of asthma in reaction to treatment, but also that none occurred for the first time after the oral treatment. However, several patients reported their previously mild asthma to be more severe this year.

Twenty-five patients in the series (30.5 per cent) experienced some degree of gastro-intestinal discomfort. Fourteen patients (17.1 per cent) experienced at some time during the treatment mild nausea or cramps. In a few cases these occurred after almost every dose, but the discomfort was not sufficient to interfere with the treatment. Ten patients (12.2 per cent) had moderately severe symptoms, characterized by severe cramps, vomiting as well as nausea, and sometimes a mild diarrhea. Three of these stopped treatment. One was the case mentioned above, and another was a middle-aged nervous woman who said in advance that medicine always made her sick. The third had her first symptoms at 30,000 units and stopped the dose immediately without returning to the clinic. The other patients were able, by

readjustment of time or size of dose, to continue without much difficulty. One patient had severe gastro-intestinal symptoms, with cramps, vomiting and diarrhea and headache, coming on for the first time after 30,000 units. Repeated reductions of the dose did not stop the reactions and the patient was finally forced to discontinue treatment when her difficulties persisted even after a dose of 8000 units.

An analysis of the factors involved in the 25 cases who failed to benefit from treatment revealed that one had pan-sinusitis during the season, while eleven gave definite evidence of other allergy or of psychogenic factors. Two were treated co-seasonally too late to expect much benefit. Three other patients had received previous

TABLE IV

Changes in reagin titers—patients treated by oral method

PATIENT	BEFORE TREATMENT	START OF SEASON	MID-SEASON	END OF SEASON
R. D.	<1:10	<1:10		<1:10
E. E.	<1:10	<1:10		<1:10
W. S.	1:320	1:320		1:320
L. Y.	1:640	1:640	1:640	1:1280
I. D.	1:80	1:80		1:160
E. W.	1:20	1:20	1:40	1:80
A. B.	1:10	1:10	1:20	1:40

injection treatment without benefit. No contributory factors were found in the other eight cases.

A small group of patients was studied to determine what effect, if any, the oral form of treatment might have on the reagin content of the serum. In seven cases blood was drawn before treatment, and at the beginning and end of the ragweed season. From three of the seven patients blood samples were also taken in mid-season. The serum was separated and kept frozen until all the samples had been collected, when all specimens from a given case were tested simultaneously on two recipients, according to the serial dilution method. Table IV shows the titers, the figures in each instance representing the highest dilution which passively sensitized the skin of a normal person to a retest with 1:100 ragweed extract. Two patients failed to show any reagin in a 1:10 dilution. One of those patients was skin

sensitive only to 1:100 ragweed, whereas the other one gave a marked reaction to a dilution of 1:5000. The other sera showed various titers: one remained unchanged throughout, one showed an increase in the last specimen, and two had increased in each of the last two specimens. In no case was there a definite change in titer between the start of treatment and the onset of the ragweed season.

SUMMARY

Eighty-two patients were treated during the summer of 1940 with ragweed pollen administered orally. Three of the patients obtained excellent relief, 10 had good results and 39 reported fair benefit. Twenty-five failed to obtain any relief, and 5 stopped treatment because of reactions. Thirty-three patients experienced some form of reaction—in 25 cases gastro-intestinal in nature. In a group of 37 patients treated hypodermically, 13 were classified as excellent, 11 as good, 9 as fair and 4 as failures. Studies of the reagin content of the serum in 7 patients failed to show any characteristic change.

CONCLUSIONS

1. Although the evidence is against the oral method as the better form of treatment of pollen hay fever, the present results seem to warrant the trial of oral treatment when circumstances are such that the patient cannot conveniently be given the injections of pollen extract.

2. Reactions, although frequent, are for the most part not severe and are fairly readily controlled. Almost all are gastro-intestinal, and no dangerous reactions have been encountered.

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FURTHER OBSERVATIONS ON THE TREATMENT OF INTRACTABLE BRONCHIAL ASTHMA BY BILATERAL RESECTION OF THE PULMONARY PLEXUS

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In 1938, the authors published a preliminary report (1) of the therapeutic results obtained in eleven cases of intractable bronchial asthma after the posterior pulmonary plexus had been resected. This operation was undertaken after all medical therapy had failed to relieve the patient; in fact, the patients who submitted to the operation were so incapacitated that they had spent most of their days and nights either in the accident room or in the wards of the hospital. The first report dealt with the operative technic, the post-operative course, and the subsequent clinical results. After reviewing the nerve supply to the lungs, the rationale for the undertaking was discussed.

Briefly, the operation is based on the fact that the extrinsic nerve supply to the lungs consists of two entirely independent tracts, which have been demonstrated by dissection (2); only by resection can this supply be completely interrupted. The nerve tracts consist of an anastomosing plexus made up of the preganglionic efferent fibers of both the vagus and the sympathetic bronchomotor tracts from the same and the contralateral sides, together with the sensory or afferent fibers emerging from the lung. The anatomic as well as the physiologic observations indicate that there is a dual nerve supply to each lung, through the vagus and also through the sympathetic trunks. In the vagus one finds mainly the bronchoconstrictor nerve fibers. In man, stimulation of the distal end of the cut vagus produces bronchoconstriction on the same side, and to a lesser degree on the opposite side. In like manner, the sympathetic nerve fibers of the same and contralateral sides are distributed to the vagus.

Bilateral interruption is necessary, therefore, to obtain what might be described as the expected physiologic result. It is well known that the mechanism involved in severe asthmatic attacks is not only a

constriction of the bronchi with the consequent increase in the resistance to inflow and outflow of air in the lungs. Constriction by spasm may play an insignificant role. There is also in the patient with chronic asthma an excessive secretion from the bronchial glands. The mucus becomes tenacious and inspissated, actually plugging both large and small bronchi, and not infrequently there is edematous swelling of the mucous membranes of the small bronchioles. These findings have been confirmed by a study of the autopsy material of 50 patients who have died in the hospitals in Boston (3) and of 25 who have died in the Johns Hopkins Hospital.

These autopsies may be divided into several groups:

First, the patients who died from the effects of anoxemia and fatigue, the direct result of *status asthmaticus*. In this group the lungs were quite rubbery and large and did not collapse when removed from the chest. Cross-section showed tough mucus plugs exuding from the bronchi. The heart showed no evidence of myocardial strain.

The second group showed definite cardiac hypertrophy, usually limited to the right side of the heart, and evidence of terminal decompensation with, however, the characteristic lung changes seen in group one. There was little emphysema; in fact, Mallory (3) states that in these two groups emphysema was rarely encountered. He found evidence of thickening of the bronchial muscles, but is of the opinion that muscle "hypertrophy" may be erroneously interpreted. He suggests that the increased diameter of the muscles in the bronchial walls is due to an unusually severe *rigor mortis*, simulating hypertrophy.

In the third group, true emphysema was encountered. The lungs were studded with areas of fibrosis, presumably the scars of previous inflammatory reaction, which surrounded minute and large areas where the air cells and respiratory bronchioles had completely ruptured. The normal elasticity of the lung structure was lacking and there was an accumulation of great quantities of mucus. Death in these cases resulted apparently from progressive decrease in the vital capacity.

The fourth group revealed classical vascular lesions of periarteritis nodosum, although not necessarily in the pulmonary tree or in the bronchial arteries. When local vascular lesions were not present within the lungs, the findings were indistinguishable from those of

ordinary bronchial asthma. The secretion was filled with eosinophiles and in the connective tissue of the lungs many eosinophile cells were present.

With this brief review of the pathology encountered, one can readily understand the difficulties which arise when a patient is considered as a possible candidate for operation. The preoperative pathologic state will, in large measure, determine the subsequent course of events. It should be emphasized at this point that all of the patients who were treated by resection of the pulmonary plexus were critically ill with an intractable disease; medical procedures failed to give even transient relief. Without resort to drastic treatment the outcome of the disease was as obvious as in any case of advanced malignant disease.

OPERATIVE RESULTS

The 21 patients treated in this clinic by resection of the pulmonary plexus may be divided into three groups for analysis.

In Group One (Chart I), the successfully treated patients, the age at the time of operation varied from 25 to 54 years. The duration of the symptoms had been from 8 months to 20 years. The interval of time elapsing between the first and second operations varied from 8 to 28 days. These patients were hospitalized for from 28 to 57 days; minor complications in several cases postponed discharge. Three of these patients were operated upon 8 years ago, two 7 years ago, one 5 years ago, and the seventh patient has been free from severe asthma for the past four years. Unfortunately, the oldest patient, 54 years of age, died 8 months after his operation. He had been incapacitated completely for one year, and four months after surgical treatment he had returned to his office with a history of mild asthma controlled by the use of an occasional hypodermic of adrenalin or by a capsule of ephedrine sulphate. The cause of death was acute cardiac dilatation.

In Group Two (Chart II) there were nine failures. The youngest of these patients was 30 years of age, the oldest was 54. All had suffered with asthma for from 6 months to 22 years. Three of the group died following the first operation; the causes of death were intrapulmonary hemorrhage, pneumonia with cardiac collapse, and post-operative empyema with subsequent coronary occlusion. Three patients died following the second operation, from acute pulmonary embolism,

CHART I

NO.	NAME	AGE AT OPERATION	DURATION OF ASTHMA	DATE OF FIRST VISIT	CAUSE OF ASTHMA	DATE OF OPERATION		TIME OF HOSPITALIZATION	INTERVAL OF TIME SINCE OPERATION	AGE OF PATIENT	FINAL RESULT
						No. 1	No. 2				
								days	*yrs.*	*yrs.*	
1	Zuloff	39	20 yrs.—at age 21	10–19–34	Intrinsic, perennial	11–15–34	11–30–34	57	8	46	100% relief
2	Wilson	32	8 yrs.—at age 24	9–25–29	Allergy: due to inhalants, intrinsic, perennial	9–28–34	10–20–34	41	8	40	Mild asthma only following respiratory infection 75%
3	Maunes	42	8 months	7–16–34	Intrinsic, perennial	6–18–35	6–28–35	28	7	49	100% relief
4	Upshaw*	25	2½ yrs.—at age 23	7– 1–36	Intrinsic, perennial	5–28–37	5–28–37*	38	5	30	Relief after 6 months 50%, controls present discomfort with adrenalin—Q.D.
5	Bruno	50	4 yrs.—at age 46	6–18–34	Intrinsic, perennial	9–12–34	9–28–34	34	8	58	100% relief
6	Smith	46	9 yrs.—at age 37	4–29–35	Intrinsic, perennial	8–23–35	8–31–35	32	7	53	50% relief
7	Twigg	50	2 yrs.—at age 48	1–13–38	Intrinsic, perennial	5–19–38	6–16–38	40	4	54	50% relief
8	Patton*	54	1 yr.—at age 53	5– 7–36	Intrinsic, perennial	3–30–37	5– 4–37*	41	Died 11–25–37, heart failure		50% relief, returned to office for 4 mos. before death

* Rt. side—section of cervical vagus.

CHART II

NO.	NAME	AGE AT OPERATION	DURATION OF ASTHMA	DATE OF FIRST VISIT	CAUSE OF ASTHMA	DATE OF OPERATION		DATE OF DEATH	CAUSE
						No. 1	No. 2		
		yrs.							
1	Foster	33	6 Mos.	11–20–35	Intrinsic, perennial	3–31–36	4–11–36	1–12–38	Died 2 years after operation—cause of death unknown
2	Kerr*	43	18 Mos.	11– 2–38	Intrinsic, perennial	11–30–38	Not done	11–30–38	Hemorrhage: autopsy—intrapulmonary
3	Cross	30	22 Yrs.	12–28–36	Intrinsic, perennial	12– 2–39	12–19–29	12–26–39	Right pulmonary embolus: autopsy
4	Hicks†	54	20 Yrs.	1– 3–34	Intrinsic, perennial	11–13–36	11–30–36	12– 7–36	Gastric distension: acute
5	Kellert‡	36	10 Yrs.	8– 4–35	Intrinsic, perennial	8– 8–35	Not done	8–14–35	Pneumonia—bronchial with cardiac collapse. No autopsy
6	Schultz	50	5 Yrs.	8– 2–32	Allergy: due to inhalants; intrinsic, perennial	2–20–36	Not done	1–24–39	Post-operative empyema complication. Death due to coronary occlusion months after operation
7	Vargus	49	15 Yrs.	6–24–37	Intrinsic, perennial	6–25–36	Also section of cervical vagus	1– 2–38	Pneumonia—18 months after operation
8	Spriggs	40	6 Yrs.	1– 9–31	Intrinsic, perennial	5–19–41	6–23–41	6–23–41	No autopsy
9	Gilbert	50	8 Yrs.	4–12–35	Intrinsic, perennial	4–11–35	5– 8–35	5– 1–36	Bronchial asthma, no autopsy

* Victim of chronic arthritis—myocardial insufficiency.

† Acute gastric distension after both operations. Cause is obscure. Was robust and should have been completely relieved. Possibly abnormal innervation caused gastrointestinal symptoms and death.

‡ Patient had bronchiectasis. Should not have been operated.

acute gastric distention, and acute intrapulmonary hemorrhage, respectively. Of this group of six patients, two died on the operating table and four died 6 to 7 days after operation. There were also in Group Two three patients who derived no relief from the operation; they died within 18 months after operation from totally unrelated causes.

The four patients in Group Three (Chart III) should not have been subjected to this radical procedure. These patients had been carefully studied in the Henry Phipps Psychiatric Clinic, and although they showed the classical signs and symptoms of violent *status asthmaticus*,

CHART III

NO.	NAME	AGE	DURATION	CAUSE	DATE OF OPERATION		RESULT
					No. 1	No. 2	
			yrs.				
1	Gilson	51	28	Psycho-neurosis	8–19–37	9– 2–39	Failure
2	McFarland	55	Severe and constant asthma her entire life	Psycho-neurosis	9–17–39	9– 7–39	Failure
3	Cornwall	29	3	Psycho-neurosis	8–31–35	9–11–35	Failure—after temporary improvement
4	Jacobson	41	3	Psycho-neurosis	6– 3–39	6–17–39	Failure

their attacks invariably followed emotional disturbances or mental strain. They continued to have the same disturbing symptoms, fortunately none the worse, following the operation. The youngest patient was 29 years of age at the time of operation and had suffered with asthma for three years; the oldest patient, who had had asthma for her "entire life," was 55 years of age.

It must be emphasized that none of the patients derived immediate relief from the operation. With one exception, all patients complained of attacks of severe asthma during the first two or three months after discharge from the hospital. Considering the autopsy findings in a large series of patients who had died following severe attacks of pro-

longed asthma, the continued attacks after operation were not unexpected. In these patients, the accumulation of pulmonary secretion might account entirely for the subsequent discomfort. Only after the cough reflex has eliminated the inspissated mucus can one expect a clearing of the asthmatic tendency following the removal of nerve influence.

It is difficult to account for all of the failures in Group Two. Of these patients, two definitely should not have been subjected to the procedure, as their general weakness made recovery quite impossible. However, several of the patients were robust negroes. In selecting patients suffering with intractable asthma for resection of the pulmonary plexus, it is impossible to set down fixed criteria for reaching the conclusion of when to, and when not to, operate. But it should be emphasized that patients in the psychogenic group should not be selected.

This group of 21 cases is presented in response to the frequent inquiries as to the merits of surgical treatment of the asthmatic patient. Before one decides upon such a radical venture, it is necessary to weigh the danger of operation against the span of life open to the patient if medical treatment has failed to give even temporary relief. However, one should not overlook the fact that the prognosis of a patient suffering with prolonged chronic asthma is comparable to the prognosis of patients with other malignant diseases.

The seriousness of the operation should not be minimized. If it is quite definitely established that no other method of medical therapy, or change of environment, is likely to give relief to the malignant asthmatic, then one would seem to be justified in advising denervation of the lungs.

SUMMARY

Twenty-one patients have been treated in this clinic by bilateral resection of the pulmonary plexus. Of these patients, eight derived striking benefit, nine died as a result of, or subsequent to, the operation, and four who failed to improve following operation are still suffering with severe bronchial asthma.

The twenty-one patients had suffered with violent attacks of asthma for periods varying from one to twenty-eight years. The duration of

the disease had no apparent effect upon the therapeutic success of the operative procedure. One patient, 39 years of age, had suffered with asthma for 20 years; since the operation 8 years ago she has never had an attack of asthma. The ages of the patients seemed to have no relation to the outcome; the youngest was 25 years of age and the oldest was 55. In every instance, these patients suffered with asthma of intrinsic type, the result of chronic respiratory infection and the subsequent infection of the pulmonary system. Allergy from extrinsic factors apparently played little part in the production of the asthmatic paroxysms.

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PROCEEDINGS OF THE MEETING OF THE JOHNS HOPKINS MEDICAL SOCIETY

HELD IN THE HURD MEMORIAL HALL, FEBRUARY 9, 1942

The President of the Society, Dr. Frank B. Walsh, presided. Abstracts and discussions of the papers follow:

Further Observations on the Treatment of Intractable Bronchial Asthma by Bilateral Resection of the Pulmonary Plexus. By LESLIE N. GAY and WILLIAM M. RIENHOFF. (Protein Clinic, Department of Medicine, and Department of Surgery.)

(Full paper published elsewhere in this number of the BULLETIN.)

DISCUSSION

Dr. Alfred Blalock asked whether or not there had been any evidence of nerve regeneration in any of the patients. He observed that it sometimes does occur in cases of sympathetic nerve operation.

Dr. Edward S. Stafford (speaking for Dr. Rienhoff who was absent) remarked that the actual technic of the operation was not difficult. He pointed out that one factor to be borne in mind before performing the operation was the vital capacity of the patient, since one lung had to be collapsed in order properly to perform the operation. Some patients who have suffered from severe asthma for a long time have very much reduced vital capacities.

Dr. Gay referred Dr. Blalock's question to Dr. Stafford, who said that there was no way of telling whether or not nerve regeneration had occurred in these patients. He said that Dr. Rienhoff generally made a rather wide separation.

Applications of the Electron Microscope to Biology and Medicine. By THOMAS F. ANDERSON. (RCA Fellow of the National Research Council, RCA Laboratories, Camden, N. J.)

In the electron microscope high velocity electrons passing through an object are focused by means of magnetic lenses to form an image of the object. The resolution obtainable is much higher than in the light microscope because, for one reason, such high velocity electrons have a much shorter wavelength than that of light (0.005 $m\mu$ as compared to 400 $m\mu$). This high resolution (of the order of 5 $m\mu$) now makes it possible to see such minute biological objects as viruses and to study their reactions in detail. Micrographs showing the sizes and shapes of plant viruses (tobacco mosaic virus, bushy stunt virus) and their reactions with antisera were shown. Vaccinia virus was shown to have definite structure. Bacteria are found to possess an outer cell wall and internal protoplasmic structure which in many cases seems to be characteristic of the organism. The combination and specificity of the reaction between flagellae and antisera was demonstrated. Ex-

tremely minute and regular details were shown in certain extracellular parts of insects such as mosquito tracheae and egg shells, as well as in the cuticle of the cockroach which had been cut into thin sections for study. Finally, the applications of the electron microscope to vertebrate anatomy were illustrated by micrographs of single nerve fibers and connective tissue fibers of the cat.

DISCUSSION

Dr. Alan M. Chesney said that he and Dr. Eagle had taken some cultures of spirochetes to Camden last year in order to have micrographs made of the organisms with the electron microscope. They found the appearance to be much the same as that observable by dark field examination with a light microscope. Dr. Chesney related the story of Dr. Bayne-Jones, who was once asked to arrange a bacteriology course for the nurses which would include "a brief demonstration of a filtrable virus."

Dr. Anderson was asked what the limits of magnification of the electron microscope are.

He replied that, as in the case of the light microscope, there was no theoretical limit to *magnification*; however, the limit of *resolution*, which is of primary interest since it determines the sharpness of the picture, now lies between 30 and 100 Å (3 to 10 mμ) in the present electron microscopes. The maximum direct magnification now obtained with the commercial RCA model is one of 60,000 times with 30 kilovolts, a relatively low voltage, or about 20,000 times with higher voltages, such as 60 kilovolts. As with the light microscope, it is more practical to take pictures at lower magnifications than the maximum, however, since the brighter image at lower magnification makes better focusing possible and shorter exposure times permissible. Also, the size of the field is greater at lower magnifications. The sharp image on the photographic plate can then be enlarged to the desired magnification in making reproductions for detailed study.

BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

Hippocratic Medicine: Its Spirit and Method. By WILLIAM ARTHUR HEIDEL. 149 pp. $2.00. *Columbia University Press, New York, 1941.*

The main theme of this work, to judge by the allotment of space, is the analysis of the scientific procedures and ideals to be found in the Hippocratic writings. Despite patently diverse elements these writings have, in the author's opinion, a common bond of rationalism and what might, in a broad sense, be called a scientific outlook. Abundant instances of the fruitful union of observation and reason and examples of the judicious use of analogy and experiment are set forth. Where there were failures—and this was not infrequently the case—the author holds that the cause was not a basic methodological shortcoming, but the complexity of the material under investigation. Indeed even today many of the strictly scientific problems discussed by the Hippocratic writers still await solution.

Shorter chapters of the book deal with the scientific and philosophic background of the fifth and fourth centuries against which the Hippocratic writings are to be viewed, and seek to give some account of the medical profession and medical practice as seen through the medium of these writings.

I find myself in agreement with the author in his discussion of the scientific aspects of the works of the Hippocratic Collection. But I cannot help feeling that an attempt to discuss the medical practice of the time entirely on the basis of these writings and a few passages from the philosophers is apt to be unrealistic and misleading. To infer very much about the average level of medical practice from the existing state of science and philosophy would be hazardous for any period and is particularly so for antiquity. The author is not unaware that the Hippocratic writings in many ways represent an ideal so far as medical practice is concerned (pp. 36, 124), but the point is not always kept in mind. It is, in any case, far too much to say (p. 6) that "medicine at any time reflects the current scientific outlook; indeed medicine is neither more nor less than the science of the day applied to the problems of health and disease."

These shortcomings need not, however, obscure the real contribution which the book makes to the study of scientific method in the Hippocratic works.

I. E. D.

Fractures. By GEORGE PERKINS. 384 pp. Illus. $6.50. *Oxford University Press, London: Humphrey Milford, 1940.*

Written in the form of a manual, and extensively illustrated by diagrams and drawings, this volume presents the highlights in the general considerations of broken bones, and thumbnail sketches of the fractures usually encountered. The author mentions the type of fracture, and in a few sentences indicates the etiology,

the signs, the methods of reduction and fixation, and the prognosis. It is remarkable that he has succeeded in presenting so many valuable facts in so concise a compendium. Naturally, because of the brevity, some important information has been excluded. As a primer in the teaching of fractures, and as a hasty reference book, this volume should serve a useful purpose.

I. W. N.